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DIRECCIÓN DE NUEVAS CREACIONES

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Bogotá, D.C.,

Abogada
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ASUNTO	Radicación	09-112457
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	07

PE - 17 2 9 0

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒	Cap. I	☒
Vía PCT (fase nacional)	☒	Cap. II	☐

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 38 a 62	9/octubre/2009
Reivindicaciones:	Folios 63 a 75	9/octubre/2009
Prioridad:	US 60/923,029	12/abril/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Métodos para preparar compuestos basados en imidazol"

El problema planteado en esta solicitud consiste en la necesidad de suministrar novedosos métodos para preparar los compuestos de fórmula I.

Para resolver este problema técnico la solicitud en estudio proporciona un método para preparar los compuestos de fórmula I.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D233/64.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 a 9 son procedimientos definidos por el producto o compuesto. Se sugiere al solicitante que defina el procedimiento de síntesis por sus etapas y condiciones, no por las características del producto a obtener.

La reivindicación 10 no es clara porque la expresión "la proporción de isómero mayor:menor de la primera mezcla es menor de la proporción de isómero mayor:menor de la segunda mezcla" es difícil de entender. Se sugiere que el señor solicitante redacte la reivindicación de forma que se entienda visiblemente la definición de la reivindicación.

La reivindicaciones 10, 23 a 25 y 28 se refieren al resultado de incrementar la proporción de isómero mayor: menor en una mezcla de los compuestos de la fórmula I, es decir, es el resultado a alcanzar luego de la aplicación de este método. La reivindicación no se puede definir por el resultado a alcanzar, porque no sólo incluye la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere al señor solicitante escribir la reivindicación de proceso solo en términos de etapas y condiciones.

A partir de la reivindicación 11 y hasta la reivindicación 21, la definición de las reivindicaciones es la misma que las reivindicaciones 1 hasta la 8, es decir la materia de la reivindicación 1 es igual a la reivindicación 11 y así sucesivamente. Se le sugiere al señor solicitante eliminar las reivindicaciones que no aporten características técnicas adicionales a la invención.

Asimismo se sugiere organizar el proceso de preparación compuestos de fórmula I de manera secuencial, mostrando de manera clara los compuestos de partida, las condiciones de reacción, las etapas de manera sistemática hasta llegar a los compuestos de fórmula I o compuestos finales, para que la reivindicación independiente supere las objeciones de claridad.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación nacional (12/abril/2007) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación	Fecha de prioridad
D1	CO-08087601	Compuestos basados en imidazol, composiciones que comprenden a los mismoa y métodos de uso	--	24/febrero/2006
D2	Journal of	A convenient synthesis of	1985	--

	organic chemistry, vol. 50, No. 7. Kim Halweg and George Büchi	2-acetyl-4(5)-(1(R),2(S),3(R),4-tetrahydroxybutyl)imidazole		
D3	Tetrahedron letters, vol. 36, no. 33. Matthew Cliff and Stephen Pyne	Asymmetric synthesis of (1R, 2S, 3R)-2- acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl) imidazole	1995	--

D1. Divulga el método para preparar el compuesto 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanoato O-metiloxima a partir de 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona y metoxilamina en presencia de HCl (Fl.40, Pág. 36).

D2 <http://www.sinab.unal.edu.co:2139/doi/abs/10.1021/jo00113a016>
Divulga un método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona (Pág. 1135, columna 2).

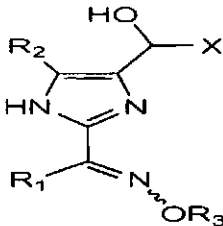
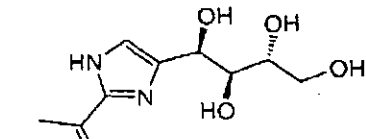
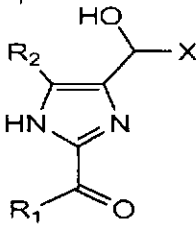
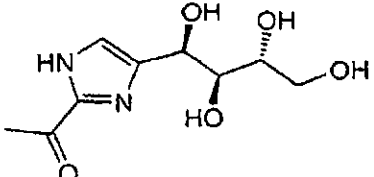
D3 <http://www.sinab.unal.edu.co:2345/doi/abs/10.1853/jo00298a123>
Divulga un método para incrementar la proporción de isómeros (E) y (Z) de derivados de imidazol, que comprende la adición de ácido (Pág. 2380).

6. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en método para preparar un compuesto de fórmula I que comprende: (Fl. 63 y 64)

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
Método para preparar un compuesto de fórmula I  que comprende:	Método para preparar un compuesto de fórmula I  que comprende:
Poner en contacto un compuesto de fórmula II  con un compuesto de fórmula III H2N-OR3 bajo condiciones suficientes para la formación de isómeros E y Z de la fórmula I	Poner en contacto un compuesto de fórmula II  con un compuesto de fórmula III H2N-OCH3 bajo condiciones suficientes para la formación de isómeros E y Z de la fórmula I

Poner en contacto la mezcla de isómeros E y Z con un ácido fuerte	Poner en contacto la mezcla de isómeros E y Z con un ácido fuerte (HCl)
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Las características **esenciales** del método para preparar un compuesto de fórmula I de la reivindicación 1 habían sido divulgadas previamente en D1, el cual enseña el método para preparar el compuesto 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanoato O-metiloxima a partir de 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona y metoxilamina en presencia de HCl (Fl.40, Pág. 36).

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado de en el documento D1.

Las reivindicaciones dependientes 2 a 8 no mencionan alguna característica que haga nueva a la composición de la reivindicación 6, por lo cual se considera que no son nuevas.

La reivindicación 40 consiste en método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona que comprende: (Fl. 72 y 73)

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D2
Método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona que comprende:	Método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona que comprende:
Agregar una primera porción de metóxido de sodio a una solución de 2-etoxiacrilonitrilo	Agregar una primera porción de metóxido de sodio (al 20%) a una solución de 2-etoxiacrilonitrilo (temperatura ambiente)
Poner en contacto con 1-amino-1-desoxi-D-fructosa	Poner en contacto con 1-amino-1-desoxi-D-fructosa (fructosamina acetato)
Agregar una segunda porción de metóxido de sodio (Temperatura 10-20°C)	Agregar una segunda porción de metóxido de sodio(al 20%v/v, a temperatura ambiente y posterior dilución con agua)
Agregar ácido acético a la mezcla	Agregar ácido acético a la mezcla
Mezclar durante un tiempo y temperatura suficiente para formar la 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona	Mezclar durante un tiempo y temperatura suficiente para formar la 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona (a temperatura ambiente, 2-3 h, rendimiento del 49%) (Pág. 1135, columna 2)

Las características **esenciales** del método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona de la reivindicación 40 habían sido divulgadas previamente en D2, el cual enseña el método para preparar 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona que comprende primero agregar una solución de metóxido de sodio al 20% a una solución de 2-etoxiacrilonitrilo a temperatura ambiente; luego adicionar fructosamina acetato; posteriormente agregar más de la solución de metóxido de sodio al 20%; diluir con agua; después adicionar ácido acético a la mezcla y por ultimo mezclar a temperatura ambiente durante 2-3 h para obtener un rendimiento del 49% de 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona (Pág. 1135, columna 2).

En consecuencia, la reivindicación 40 carece de novedad, según lo divulgado de en el documento D2.

Las reivindicaciones dependientes 41 a 48 no mencionan alguna característica que haga nueva a la composición de la reivindicación 40, por lo cual se considera que no son nuevas.

Nivel Inventivo (Art18 D486)

La reivindicación 28 consiste en un método para incrementar la proporción de isómero E:Z en una mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima, que comprende: (Fl. 70 y 71)

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D3
Método para incrementar la proporción de isómero E:Z en una mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima, que comprende:	Método para preparar una mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima, que comprende:	Método para incrementar la proporción de isómeros (E) y (Z) de derivados de imidazol, que comprende:
Poner en contacto una solución que comprende una primera mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima con un ácido fuerte bajo condiciones suficientes para proporcionar una segunda mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima en donde la proporción de isómero E:Z de la primera mezcla es menor que la proporción de isómero E:Z de la segunda mezcla	Poner en contacto una solución que comprende una primera mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima con un ácido fuerte Fl. 40	Poner en contacto los derivados de imidazol con un ácido fuerte bajo condiciones suficientes para proporcionar mezcla de los isómeros (E) y (Z) Pág. 2380

Los documentos D1 y D3 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan métodos para incrementar la proporción de isómero E:Z en una mezcla.

D1 da a conocer un método para preparar la proporción de isómero E:Z en una mezcla de (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima y (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima (Fl.40).

D3 divulga un método para incrementar la proporción de mezcla de isómeros E y Z de derivados de imidazol.

La diferencia entre la invención, definida en la reivindicación 28 y el método del documento D1 consiste en que la invención manifiesta el incremento de los isómeros.

La diferencia entre la invención, definida en la reivindicación 28 y el método del documento D3 consiste en que la invención tiene los isómeros del compuesto 1-(4-((1R,2S,3R)-1,2,3,4-tetrahidroxibutil)-1H-imidazol-2-il)etanona oxima.

No se evidencia que por el hecho de manifestar el incremento de los isómeros, se tenga un efecto técnico inesperado.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el propósito del método de preparación de isómeros del documento D1 para conseguir métodos alternativos".

Sin embargo, es conocido en el documento D3, que el incremento en la proporción de isómeros E y Z, se consigue por el contacto con un ácido fuerte. Adicionalmente es conocido que el contacto con el ácido permite obtener una proporción adecuada de la mezcla de isómeros de acilimidazol; luego pueden separarse por cromatografía de intercambio iónico.¹

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a emplear el método de preparación de derivados de imidazol que utiliza ácido fuerte para aumentar la proporción de la mezcla de isómeros.

Conclusión:

La reivindicación 28 no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 29 a 39 no mencionan características inventivas adicionales, tampoco se pueden considerar inventivas.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	CO-08087601	1 a 8 28 a 39	Novedad Nivel inventivo
D2	Journal of organic chemistry, vol. 50, No. 7. Kim Halweg and George Büchi	40 a 48	Novedad
D3	Tetrahedron letters, vol. 36, no. 33. Matthew Cliff and Stephen Pyne	28 a 39	Nivel inventivo

¹ Udo Kroeplien . US 4567194. 2-Acylimidazole compounds, their synthesis and use as medicinal agents. 28 junio 1986. Columna 12.
<http://www.google.com/patents/US4567194?pg=PA9&dq=US+4567194&hl=en&sa=X&ei=AxRULWUEJLQ8wTkzYGI&ved=0CC8Q6AEwAA#v=onepage&q&f=false>

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
02 OCT. 2012

Elaborado por: Ruth Angélica Lizarazo Pedraza 
Revisado por: Consuelo Leguizamón Leguizamón

acetal. This reaction parallels the previously reported acetalization of 2-formylimidazole in acidified ethanol.¹³ In all acidified solvents containing exchangeable deuterium (DCl, D₂O), rapid exchange of the methyl protons with deuterium was observed.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr pellets, on a Perkin-Elmer Model 281 IR spectrometer. Polarimetric measurements were done on a Perkin-Elmer Model 241 polarimeter. The ¹H NMR and ¹³C NMR spectra were acquired in the FT mode, using a Bruker CXP-300 spectrometer at the frequencies of 300 and 75.46 MHz, respectively. Chemical shifts are given in ppm downfield from Me₄Si. The internal standard for ¹H in Me₂SO-*d*₆ was tetramethylsilane (Me₄Si). The internal standards used for ¹³C in various solvents were D₂O (*p*-dioxane, 67.4 ppm), Me₂SO-*d*₆ (Me₂SO-*d*₆, 39.5 ppm), CD₃OD (CD₃OD, 49.0 ppm). Abbreviations used are s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; mult, multiplet. Multiplicities for the ¹³C resonances were determined by off-resonance decoupling. Elementary analyses were done by Atlantic Microlab Inc., Atlanta, GA. Chromatography fractions were analyzed at a wavelength of 250 nm on a Tracer HPLC using a C₁₈ μ -Bondapak column, Waters Radial Pak, with MeOH (10%), AcOH (0.5%), H₂O (89.5%) as eluant at a flow rate of 1 mL/min. Compound 6 had a retention time of 20 min and compound 1 5.5 min under these conditions.

D-Glucosone (4). A mixture of 13.4 g (37.4 mmol) of D-glucose phenyllosazone,¹² 400 mL of ethanol, 667 mL of H₂O, 16.4 mL of glacial acetic acid, and 21.4 mL (210 mmol) of freshly distilled benzaldehyde was heated at reflux under N₂ until solution was complete (approximately 4.25 h). With continued heating, 400 mL of the solution was distilled off while an equal volume of water was added dropwise. The resulting mixture was allowed to stand under N₂ overnight. The precipitate of benzaldehyde phenylhydrazone was removed by filtration and the filtrate concentrated in vacuo (<40 °C) to 400 mL. This solution was in turn extracted with 4 $\times$ 150 mL ether and decolorized with charcoal. The resulting yellow solution was evaporated to dryness (<40 °C) and the concentrated syrup was taken up in 100 mL of ethanol. Then, 5 g of mixed bed ion-exchange resin was added and the mixture filtered and again evaporated to dryness to give a thick oil, 4.6 g (25.8 mmol, 69%).

4-(1,2,3,4-Tetrahydroxybutyl)-2-acetyl-1-imidazole Ethylene Dithioketal (6). A mixture of the above glucosone (4.6 g, 25.8 mmol), 2-methyl-1,3-dithiolane-2-carboxaldehyde⁵ (5; 15.0 g, 101 mmol), and 125 mL of methanol was stirred at room temperature until solution was complete; then 20.0 g of ammonium acetate was added and the mixture was stirred at room temperature for 18 h.

The entire reaction mixture was poured into 600 mL of H₂O (10 mL of 1 N HCl added) and extracted with 4 $\times$ 200 mL of ether. [By redistilling the ether extract, 50% of the original pyruvaldehyde thioacetal can be recovered.] The resulting aqueous layer was added to a 40 $\times$ 3.5 cm Rexyn (poly(styrenesulfonic acid)) column in the H⁺ form and the column washed with 1 L of water. The imidazole fraction was then isolated by washing the column with 1 L of cold 4 M NH₄OH solution.

Evaporation of the ammonia extract gave a thick oil, which was purified by washing through an open 15 $\times$ 3.5 cm C₁₈ μ -Bondapak column, using 0.5% HOAc-H₂O as eluant. Combining the proper fractions after HPLC analysis and evaporation afforded 2.36 g of 6 as the acetate salt, thick oil (7.7 mmol, 30%). Trituration from EtOH-Et₂O afforded an amorphous solid: mp 148–51 °C; IR (KBr) 3360 (s), 3120 (s), 2920 (s), 1620 (w), 1570 (w), 1470, 1420 (s), 1365, 1305, (w), 1275 (w), 1195, 1110, 1090 (s), 1060 (s), 990 (s), 880 cm⁻¹; NMR (as the acetate salt) ¹³C (D₂O) 151.99 (C2, s), 136.47 (C4, s), 117.20 (C5, d), 73.73, 71.79, 65.90 (CHOH, d), 63.67 (CH₂OH, t) 60.01 (–C(S)₂, s), 41.48 (CH₂S, t), 29.35 (CH₃, q) (acetic acid gave peaks at 22.60 (q) and 179.59 (s)); ¹H (CD₃OD) 1.74 (CH₃C(S)₂, s), 3.08–3.09 (SCH₂S, mult), 3.18–3.40 (HCO, H₂CO, mult), 4.51 (IM- α HCO, dd), 8.45 (C5H, d); UV ($\lambda_{\max}$, log ϵ) 226 nm, 3.92 (H₂O, pH 7.0).

2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)imidazole (1). To a solution of 2.36 g (7.7 mmol) of 6 acetate salt in 25 mL of H₂O

was added 3.0 g (17.6 mmol) AgNO₃ in 25 mL of H₂O. The mixture was stirred at room temperature for 18 h in the dark, after which time 1.5 mL of concentrated HCl was added and the solution was stirred for an additional 10 min. The AgCl was removed by filtration through a bed of Celite 540 and the filtrate was then passed through a 15 $\times$ 2.5 cm C₁₈ μ -Bondapak column. The column was washed with water until all of the product (HPLC analyzed) had eluted.

The combined eluant was then passed through a 15 $\times$ 2.5 cm Bio-Rad AG1X2 anion exchange resin in the OAc⁻ form and the eluate was concentrated to 50 mL in vacuo. After 48 h at 5 °C, the resulting crystals were removed by filtration and dried in vacuo to give 684 mg (two crops, 2.97 mmol, 39%) of 1; recrystallized from H₂O (charcoal); mp 232–3 °C (soften at 224 °C); [α]_D²⁵ –12° (c 1.17, 1 N HCl); UV ($\lambda_{\max}$, log ϵ) 289 nm, 4.11 (H₂O, pH 7.0). IR (KBr) 3450, 3320, 3290, 3020, 1665, 1655, 1455, 1435, 1405, 1380, 1255, 1220, 1090, 1020, 955, 880, 790, 645 cm⁻¹. Anal. Calcd. for C₉H₁₄N₂O₅: C, 46.96; H, 6.09; N, 12.17. Found: C, 46.31; H, 6.12; N, 12.05.

NMR: ¹³C (D₂O, DCl, pH <2) 27.57 (CH₃C(O)–, q), 64.19 (CH₂OH, t), 66.22, 72.08, 74.09 (CHOH, d), 120.62 (C5, d), 139.10 (C4, s), 140.54 (C2, s) and 186.27 (C=O, s); ¹³C (Me₂SO-*d*₆, free base) 2 tautomers A and B [A] 25.28 (CH₃C(O), q), 63.49 (CH₂OH, t), 67.10, 71.22, 73.73 (CHOH, d), 119.01 (C5, d), 143.73, 146.72 (C2 and C4, s), 188.26 (C=O, s); [B] 25.05 (CH₃C(O), q), 63.25 (CH₂OH, t), 64.69, 71.22, 73.73 (CHOH, d), 127.92 (C5, d), 139.12, 144.26 (C2, C4, s), 188.15 (C=O, s); ¹H (Me₂SO-*d*₆, free base) 2-tautomers A and B [A + B] 2.47, 2.48 (CH₃C(O), s), 3.35–3.80 (HCO, H₂CO, mult), 4.30–4.39, 4.58–4.64, 5.01–5.04 (COH, mult), 4.90–4.92 (IM- α HCO, mult), 7.05, 7.21 (C5H, d); ¹³C (Me₂SO-*d*₆, DCl, pH <2) 27.09 (CH₃C(O), mult partially deuterated), 63.57 (CH₂OH, t), 65.14, 71.27, 73.20 (CHOH, d), 119.46 (C5, d), 138.71, 139.55 (C2, C4, s), 183.98 (C=O, s); ¹H (Me₂SO-*d*₆, DCl, pH <2) one tautomer 2.66 (CH₃CO, s), 3.42–3.56 (HCO, H₂CO, mult), 5.06 (IM- α HCO, dd), 7.67 (C5H, d); ¹³C (CD₃OD, DCl, pH <2) after standing in CD₃OD, DCl for 12 h 23.21 (CH₃C partially deuterated mult), 64.76 (CH₂OH, t), 66.28, 72.62, 74.69 (CHOH, d), 99.05 (C(O)C, s), 117.20 (C5, d), 137.88, 147.97 (C2, C4, s); ¹H (CD₃OD, DCl, pH <2) standing in CD₃OD, DCl for 12 h, 1.71 (CH₃CO₂, mult partially deuterated), 3.60–3.83 (HCO, H₂CO, mult), 5.12 (IM- α HCO, dd), 7.39 (C₅H, d).

Acknowledgment. We thank Dr. U. Kröplien, Coca-Cola G.m.b.H., Essen, FRG, for sharing in advance his unpublished results on the isolation of 1 from ammonia caramel. We also extend our appreciation to Dr. Jacob H. Goldstein, Chemistry Department, Emory University, for helpful discussions.

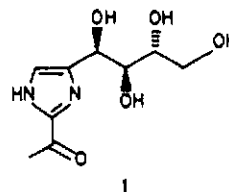
A Convenient Synthesis of 2-Acetyl-4-(5)-(1(R),2(S),3(R),4-tetrahydroxybutyl)-imidazole

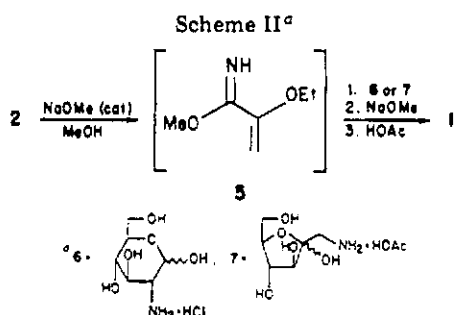
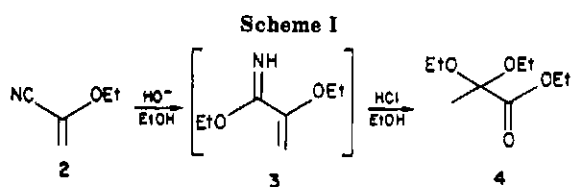
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Received October 9, 1984

The title compound (1), a very minor constituent of Caramel Color III lowers circulating lymphocyte counts when fed to rats.





Kröplien¹ and co-workers who isolated and determined the structure of this imidazole (1) found that it was formed in approximately 1% yield in the reaction of fructosamine acetate, pyruvaldehyde, and aqueous ammonia. This synthesis provided the first evidence that the relative and absolute configuration of the tetrahydroxybutyl side chain was identical with that present in glucose, a finding that did not cause much surprise because caramels are prepared from glucose. This finding was later verified in a second,² more efficient synthesis of the factor in which D-glucosone, pyruvaldehyde dithioketal, and ammonia were condensed to yield the dithioketal of the 2-acetylimidazole 1. The capricious hydrolysis of the dithioketal protecting group was best accomplished with excess aqueous silver nitrate. In this paper, we disclose a very simple synthesis of 1.

Cuvigny reported that 2-ethoxyacrylonitrile (2) could be prepared by bromination of ethyl vinyl ether followed by treatment with cuprous cyanide and dehydrobromination with diethylamine.³ This three-step synthesis proceeded in an overall yield of 49% and did not require isolation of intermediates. Exposure of 2 to ethanol in alkaline media generated an intermediate which upon treatment with acidic ethanol produced ethyl 2,2-diethoxypropionate (4) (Scheme I).⁴ This intermediate was tentatively assumed to be ethyl 1-ethoxyvinylimidate (3) on the basis of the structure of its ethanolysis product 4 and the fact that it was shown not to be the 1,4-adduct 2,3-diethoxypropionitrile nor 2,2-diethoxypropionitrile, both of which were prepared by independent syntheses.

We reasoned that imidates such as 3 would be ideal intermediates for the synthesis of 1 since they allow for protection of the acetyl substituent as an enol ether and contain the imide functionality which is known to generate imidazoles upon treatment with α -amino carbonvls.⁵

It was found that both D-(+)-glucosamine hydrochloride (6), which is commercially available, or 1-amino-1-deoxy-D-fructose acetate (7),⁶ prepared from glucose in nearly quantitative yield by treatment with dibenzylamine followed by hydrogenation, can serve as the required α -amino carbonyl component.

A very convenient one-pot synthesis of 1 from readily available starting materials is outlined in Scheme II. A methanolic solution of 2-ethoxyacrylonitrile (2) containing a catalytic amount of sodium methoxide was stirred overnight at room temperature to generate what was assumed to be methyl 1-ethoxyvinylimidate (5).⁷ Either glucosamine hydrochloride (6) or fructosamine acetate (7) was added followed by a total of 1 equiv of sodium methoxide. After stirring at room temperature for 2-3 days, the starting amino sugars were consumed. Since the free base of 1 is insoluble in water², and strongly acidic conditions are required to form the corresponding imidazolium salt, it was hoped that precipitation of the free base from water would prove to be a convenient workup procedure. Thus, dilution with water, acidification with acetic acid (to hydrolyze the enol ether), and removal of the methanol in vacuo induced precipitation of a light yellow solid. This material was collected by filtration and recrystallized from water to give the desired imidazole 1, identical with the material isolated from ammonia caramel¹ and with that obtained by the alternate synthesis mentioned above.²

This reaction sequence (Scheme II) proceeds in a 46% overall yield with fructosamine acetate 7 or 19% yield with the commercially available glucosamine hydrochloride (6). Due to the availability of starting materials and the brevity of this synthesis, 2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (1) can now easily be prepared in multigram quantities.

Experimental Section

Melting points were determined with a Büchi SMP-20 capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 283B spectrophotometer and ^1H NMR and ^{13}C NMR spectra were recorded with a JEOL Model FX 90Q spectrometer. Optical rotations were obtained with a Perkin-Elmer Model 141 polarimeter at the sodium D line at ambient temperature. Ultraviolet spectra were recorded with a Perkin-Elmer Hitachi 200 spectrophotometer.

Reagent-grade anhydrous methanol was purchased from Mallinckrodt and used without purification. 2-ethoxyacrylonitrile³ and 1-amino-1-deoxy-D-fructose acetate⁶ were prepared as reported. D-(+)-Glucosamine hydrochloride was purchased from Aldrich and used directly.

General Procedure for the Preparation of 2-Acetyl-4-(5)-(1*R*),2(*S*),3(*R*),4-tetrahydroxybutyl)imidazole (1). A 1.93 M solution of sodium methoxide in methanol (0.71 mL, 1.37 mmol) was added to a solution of 2-ethoxyacrylonitrile (2) (1.34 g, 13.80 mmol) in 30 mL of methanol and stirred overnight at room temperature. This solution was diluted with 20 mL of methanol and cooled to -5 °C, and the appropriate amino acid sugar (13.77 mmol) was added in one portion. After 20 min a solution of 1.93 M sodium methoxide in methanol was added (2.14 mL, 4.13 mmol) and the mixture was warmed to room temperature over a 2-h period and stirred overnight. The mixture was cooled to -5 °C and a 1.93 M solution of sodium methoxide in methanol (5.00 mL, 9.65 mmol) was added. The resulting mixture was allowed to warm to room temperature over a 2-h period and stirred for 2-3 days. Filtration of the reaction mixture was followed by dilution with 20 mL of water and addition of glacial acetic acid (0.7 mL, 12.23 mmol). After 30 min the solution was concentrated in vacuo to a volume of approximately 10 mL until precipitation began. The mixture was allowed to stand overnight at room temperature and the solid was collected by filtration. Recrystallization from water gave 1 as a crystalline solid: mp 234-236 °C; $[\alpha]_D^{25}$ -10 °C (c 1.00, 1 N HCl); UV_{max} (H₂O) 289 nm (log ϵ 4.14), 215 (3.36) (sh); IR (KBr) 3460, 3290, 3020, 1660, 1380, 1255, 1220, 1090, 1025, 955, 940, 930, 790, 650 cm⁻¹; ¹H NMR (D₂O, DCl) δ 2.74 (s, 3 H), 3.64-3.92 (m, 4 H), 4.96 (br s, OH protons and H₂O), 5.29 (br s, 1 H), 7.68 (s, 1 H); ¹³C NMR (D₂O, DCl) δ 28.26, 64.58, 66.44, 72.38,

(7) Method of Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* 1961, 26, 412.

(1) Kröplien, U.; Rosdorfer, J.; van der Greef, J.; Long, R. C., Jr.; Goldstein, J. H. *J. Org. Chem.*, first paper in a series of three in this issue. References to biological studies are given in this paper.

(2) Sweeney, J. G.; Ricks, E.; Estrada-Valdés, M. C.; Iacobucci, G. A.; Long, R. C., Jr. *J. Org. Chem.*, preceding paper in this issue.

(3) Cuvigny, T. *Ann. Chim. Paris* 1956, 1, 475.

(5) Ellinger, L. P.; Goldberg, A. A. *J. Chem. Soc.* 1949, 263.

(6) Hodge, J. E.; Fisher, B. E. in "Methods in Carbohydrate Chemistry"; Whistler, R. L., Wolfrom, M. L., Bemiller, J. N., Eds.; Academic Press: New York, 1963; Vol. II, pp 99-103.

74.33, 120.96, 139.25, 140.59, 186.27.

Preparation of 1 from 2-Amino-2-deoxy-D-(+)-glucose Hydrochloride (6). The general procedure was followed by using 2-amino-2-deoxy-D-(+)-glucose hydrochloride (2.97 g, 13.77 mmol). After the final addition of sodium methoxide stirring was continued for 2 days at room temperature. Typical workup (vide supra) gave 0.60 g (19%) of 1.

Preparation of 1 from 1-Amino-1-deoxy-D-fructose Acetate (7). The general procedure was followed by using 1-amino-1-deoxy-D-fructose acetate (3.30 g, 13.77 mmol). After the final addition of sodium methoxide stirring was continued for 3 days at room temperature. Typical workup (vide supra) gave 1.46 g (46%) of 1.

Acknowledgment. We are grateful to the International Technical Caramel Association for financial support. We thank Dr. U. Kröplien, Coca-Cola G.m.b.H, Essen, FRG, for helpful discussions in the early stages of this work, and Dr. J. Sweeny of the Coca-Cola Company, Atlanta, GA, for useful information concerning the solubility properties of 1.

Registry No. 1, 94944-70-4; 2, 19479-65-3; 6, 66-84-2; 7, 6333-49-9.

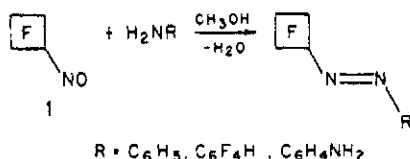
Synthesis and Structure Determination of 3,3,4,4-Tetrafluoro-N-methyl-2-(*cis,s-trans*-methyl-NNO-azoxy)-*s-cis*-1-cyclobutene-1-amine¹

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David P. Shoemaker,^{2b} Helen M. Marsden,^{2c,3} and
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Received September 18, 1984

The reactions of nitroso compounds with primary amines normally result in the formation of azo compounds, with concomitant elimination of water.^{4,5} Recently there has been renewed interest in the reaction of CF₃NO with aromatic amines as a route to the introduction of trifluoromethyl groups into these molecules via azo intermediates.⁶⁻⁸ In this context, we studied the reactions of heptafluoronitrosocyclobutane (1) or nonafluoronitrosocyclopentane (2) with several primary amines. The expected condensation reactions occurred to form the azo products.¹⁰ Corresponding reactions occur with 2. How-



(1) *Cis* and *trans* are based upon Cahn-Ingold-Prelog priorities for fluorine and nitrogen.

(2) (a) University of California, Davis. (b) Oregon State University. (c) University of Idaho.

(3) American Association of University Women International Fellow, 1982-83.

(4) Makarov, J. P.; Yakubovich, A. Ya.; Ginsburg, V. A.; Filatov, A. S.; Englin, M. A.; Privezentseva, N. F.; Nikoforova, T. Ya. *Dokl. Akad. Nauk SSSR* 1961, 141, 357.

(5) Ginsburg, V. A.; Vasil'eva, M. N. *Zhur. Org. Khim.* 1973, 9, 1080.

(6) de Meijere, A.; Goltz, P. *Angew. Chem., Int. Ed. Engl.* 1977, 16, 854.

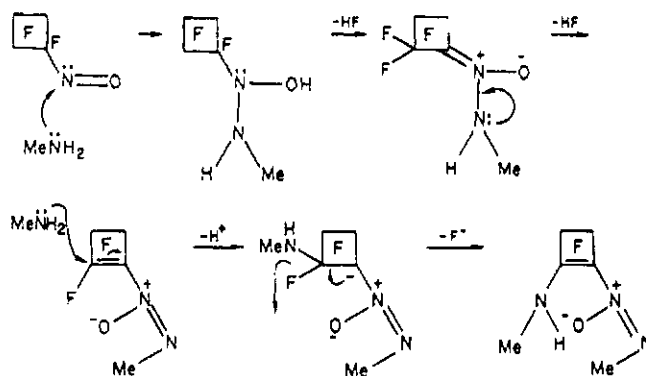
(7) Hartkopf, U.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* 1982, 21, 443.

(8) Umamoto, T.; Miyano, O. *Tetrahedron Lett.* 1982, 23, 3929.

(9) Umamoto, T.; Sekiya, A. *Chem. Lett.* 1982, 1519.

(10) Marsden, H. M.; Shreeve, J. M. *Inorg. Chem.* 1984, 23, 3654; *J. Fluorine Chem.* 1985, 27, 275.

Scheme I



ever, when methylamine is used instead of the aromatic amines the reaction takes a quite different and intriguing path. Although CF₃N=NCH₃ is the high-yield product from the reaction of CH₃NH₂ with CF₃NO,¹¹ no azo compound is obtained from the reaction of methylamine with 1. Instead, a sublimable, crystalline product with the empirical formula C₆H₇F₄N₃O is formed. A firm structural assignment from spectroscopic data was difficult. The correct structure was determined by X-ray methods, showing that the compound is 3 which may result via the mechanism in Scheme I.

The elimination of HF, leading to an azoxy compound, is preferred to the loss of H₂O which would result in the formation of an azo material. The electron shift to form the stable conjugated azoxybutene system aids the attack of the methylamine at the more positive carbon, followed by further loss of HF to give the isolated product.

Although electrophilic fluorinated nitrosoalkanes have been reacted with dozens of aliphatic, alicyclic, and aromatic compounds that contain the nucleophilic NH₂ group, no evidence has been found for the formation of azoxy compounds in addition to the expected azo materials.¹¹ It should be noted that the analogous azoxy product was formed when 2 was reacted with methylamine. The existence of the latter was demonstrated by comparing the ¹H and ¹⁹F NMR, UV, IR, MS, and elemental analysis data with those of 3 whose structure is reported in this paper.

Experimental Section

All reagents were used as received from commercial suppliers. Methylamine was obtained from Matheson. Heptafluoronitrosocyclobutane and nonafluoronitrosocyclopentane were prepared by literature methods.¹⁰

Gases and volatile liquids were handled in a conventional Pyrex glass vacuum system equipped with a Heise Bourdon tube gauge and a Televac thermocouple gauge. Starting materials were measured quantitatively by PVT techniques. Spectrometers used were IR, Perkin-Elmer 599; ¹⁹F and ¹H NMR, JEOL FX-90Q FT at 84.26 and 90 MHz, or Varian EM-360L at 54.6 MHz; MS, Hitachi Perkin-Elmer RMU-6E at 17 eV; UV, Beckman Acta MVII, scanning from 250 to 800 nm, using CHCl₃ solutions contained in 1-cm cuvettes. For the NMR studies, CDCl₃ and/or CFCI₃ were used as solvents and as internal or external references; ¹⁹F chemical shifts upfield from that of CFCI₃ were assigned negative values. For IR, KBr disks were employed. Elemental analyses were by Beller Mikroanalytisches Laboratorium, Göttingen, FRG.

1 (6 mmol) and methylamine (8 mmol) were added to methanol (10 mL, liquid N₂ temperature) in a 250-mL round-bottomed flask equipped with a 19/26 inner ground glass joint to which was attached a Kontes Teflon-brand stopcock. The flask was then

(11) Dinwoodie, A. H.; Haszeldine, R. N. *J. Chem. Soc.* 1965, 2266. (An azoxy compound is reported (2% yield) but it is a hydrolysis product [CF₃N(O)NCF₃] of CF₃NO and not the methyl(trifluoromethyl) derivative [CF₃N(O)NCH₃].)

121

Asymmetric Synthesis of 2-Acetyl-4(5)-(1,2,4-trihydroxybutyl)imidazoles

Matthew D. Cliff and Stephen G. Pyne*

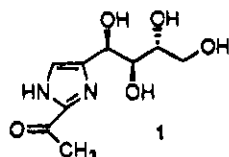
Department of Chemistry, University of Wollongong, Wollongong, New South Wales 2522, Australia

Received December 13, 1994*

A method for preparing trihydroxybutyl analogues of the biologically active compound 2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) is reported. This method employs a palladium(0)-catalyzed coupling of 1-(ethoxymethyl)-4-iodoimidazole (**3a**) to functionalized vinylstannane **11**, 1-alkynylstannane **16**, or alkyne **10** to introduce the C-4 imidazole 4-carbon side chain. The 1,2-dihydroxy functionality of the butyl side chain was introduced by a Sharpless catalytic asymmetric dihydroxylation.

Introduction

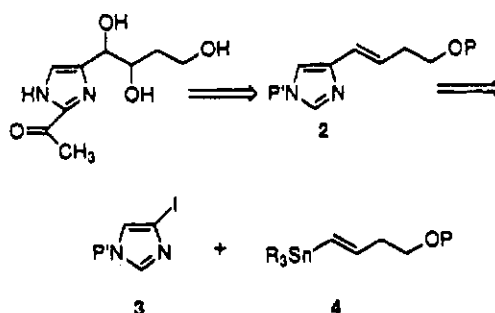
2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI, **1**), a constituent of caramel color III, has been found to depress blood lymphocyte counts in both mice and rats.¹



THI produces lymphopenia, apparently without toxic effects, in rats and mice and is able to affect the immune competence in the rat in quite small quantities (e.g., 1–50 ppm in drinking water).² THI has also been reported to prevent spontaneous and cyclophosphamide-induced diabetes in nonobese diabetic mice.³ To investigate the structure–activity relationships of this structurally simple but biologically intriguing molecule we desired a general and flexible synthesis of THI analogues. Three syntheses of THI have been reported, and these all rely on the use of glucose derivatives to prepare the 1,2,3,4-tetrahydroxybutyl side chain.^{4–6} These syntheses are either not sufficiently flexible for the synthesis of THI analogues⁶ or suffer from poor overall yields.^{4,5}

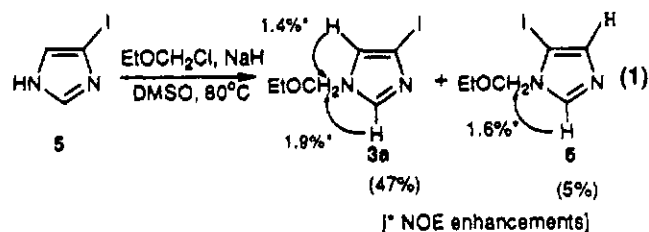
We report here a new synthetic protocol for the synthesis of 1,2,4-trihydroxybutyl THI analogues as outlined in Scheme 1. This involves a palladium-catalyzed coupling of a 1-protected 4-iodoimidazole **3** to a functionalized vinylstannane **4** to produce the alkene **2**, followed by a Sharpless catalytic asymmetric dihydroxylation (AD) to introduce the 1,2-dihydroxy functionality into the butyl side chain (Scheme 1). We chose the ethoxymethyl (EtOCH₂) protecting group for the imidazole nitrogen since this group would assist the introduction of the 2-acetyl group into the imidazole ring later in the synthesis.⁷

Scheme 1



Results and Discussion

Treatment of 4-iodoimidazole⁸ (**5**) with sodium hydride and chloromethyl ethyl ether in DMSO at 80 °C⁹ gave a 91:9 mixture of 1-(ethoxymethyl)-4-iodoimidazole (**3a**) and 1-(ethoxymethyl)-5-iodoimidazole (**6**). These isomeric compounds were separated by column chromatography, and their structures were evident from 1D NOE difference experiments (eq 1).¹⁰



Hack-type coupling reactions^{11,12} between models of **3a** (i.e., 1-*p*-tosyl-4-iodoimidazole (**3b**) or 1-trityl-4-iodoimidazole (**3c**)⁸ and 4-[(*tert*-butyldimethylsilyl)oxy]-1-butene (**7**) failed to give any of alkene **8**. Only 4,4'-biimidazoles **9** were isolated (eq 2).¹³

(7) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

(8) Kirk, K. L. *J. Heterocycl. Chem.* **1985**, *22*, 57. Iddon, B.; Lan Lim, B. *J. Chem. Soc., Perkin Trans. 1* **1988**, 735.

(9) Kashima, C.; Harada, Y.; Hosomi, A. *Heterocycles* **1983**, *35*, 433. (10) Colombo, R.; Colombo, F.; Derome, A. E.; Jones, J. H.; Rathbone, D. L.; Thomas, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1811.

(11) Heck, R. F. *Org. React.* **1982**, *27*, 345. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: Orlando, 1985.

(12) Heck coupling of 4-iodoimidazoles has not been previously reported.

(13) 4,4'-Biimidazoles are also isolated in good yield in the absence of the alkene: Cliff, M. D.; Pyne, S. G. *Synthesis* **1994**, 681.

* Abstract published in *Advance ACS Abstracts*, April 1, 1995.

(1) Iscaro, A.; Mackay, I. R.; O'Brine, C. *Immunol. Cell. Biol.* **1988**, *66*, 395.

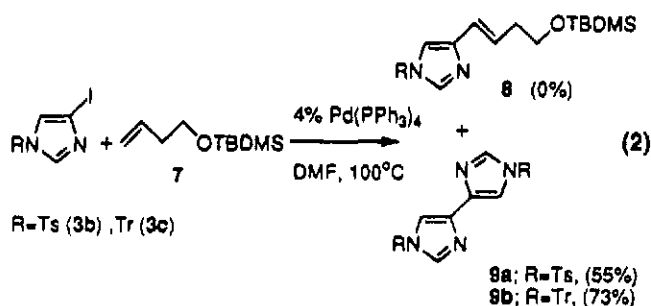
(2) Golin, S. J. P.; Phillips, J. A. *Clin. Exp. Immunol.* **1991**, *85*, 335.

(3) Mandel, T. E.; Koulmanda, M.; Mackay, I. R. *Clin. Exp. Immunol.* **1992**, *88*, 414.

(4) Kroplien, U.; Rosdorfer, J.; Vander Geef, J.; Long, R. C., Jr.; Goldstein, J. H. *J. Org. Chem.* **1985**, *50*, 1131.

(5) Sweeny, J. G.; Ricks, E.; Estrada-Valdes, M. C.; Iacobucci, G. A.; Long, R. C., Jr. *J. Org. Chem.* **1985**, *50*, 1133.

(6) Halweg, K. M.; Buchi, G. *J. Org. Chem.* **1985**, *50*, 1134.

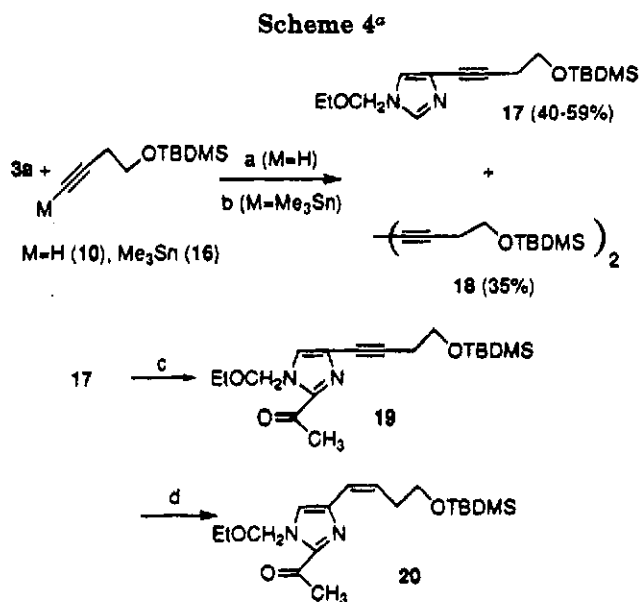
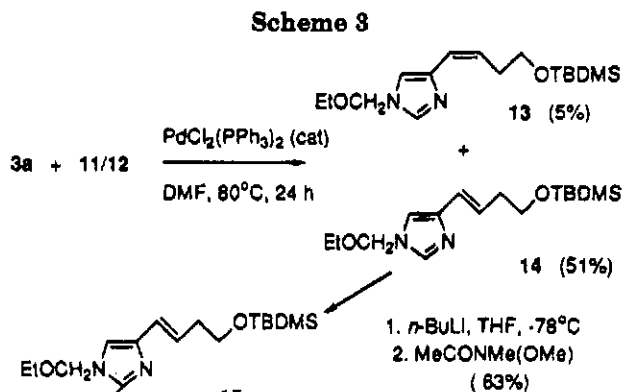
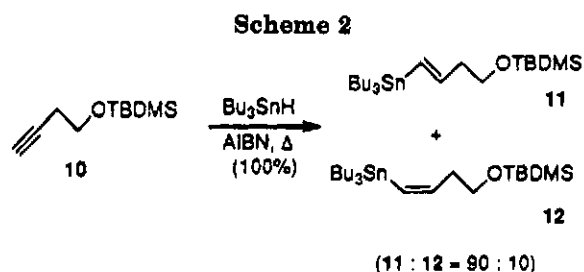


Consequently, Stille-type coupling reactions of **3a** and vinylstannanes were investigated.¹⁴⁻¹⁶ Hydrostannylation¹⁷ of 4-[(*tert*-butyldimethylsilyl)oxy]but-1-yne (**10**) at 120 °C gave an inseparable 90:10 mixture of the (*E*)- and (*Z*)-vinylstannanes **11** and **12** in quantitative yield (Scheme 2). Lower reaction temperatures gave more of the (*Z*)-isomer.

Treatment of iodoimidazole **3a** with a 81:19 mixture of **11** and **12** (1.05 equiv, prepared from the hydrostannylation of **10** at 80 °C) in the presence of PdCl₂(PPh₃)₂¹⁸ (5 mol%) in DMF gave a mixture of the desired alkene adducts **13** and **14** in 5% and 51% yields, respectively (Scheme 3). Treatment of **14** with *n*-butyllithium in THF at -78 °C followed by quenching the resulting 2-lithioimidazole derivative with *N*-methoxy-*N*-methylacetamide¹⁹ (-78 °C to rt) gave the 2-acetylimidazole **15** in 63% yield. Other acetylating agents, for example, acetic anhydride and *N,N*-dimethylacetamide, were not effective.

Alternatively the (*Z*)-alkene **13** could be prepared stereoselectively from **3a** in two steps (Scheme 4). The palladium(0)-catalyzed coupling of **3a** and **10** (1.5 equiv) in the presence of copper(I) iodide and triethylamine in acetonitrile at reflux²⁰⁻²² gave alkyne **17** in 40% yield based on iodoimidazole **3a** and the dialkyne **18** (35% based on **10**), formed from the homocoupling of **10** (Scheme 4). A better yield (59%) of **17** could be realized from the palladium(0)-catalyzed coupling of **3a** and the 1-(trimethylstannyl)alkyne **16** in DMF at 80 °C (Scheme 4).^{14,23} The alkyne **17** was converted to the 2-acetyl derivative **19** as described above. Catalytic hydrogenation of **19** over Lindlar's catalyst²⁴ in the presence of quinoline gave the (*Z*)-alkene **20** in 83% yield.

Asymmetric Dihydroxylations. Catalytic asymmetric dihydroxylation (AD) of **15** at 0 °C for 4 days using



(14) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(15) For a recent review on the palladium-catalyzed coupling reactions of heterocyclic compounds see: Kalinin, V. N. *Synthesis* **1992**, 413.

(16) Stille coupling of 4-iodoimidazole has not been previously reported.

(17) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Ya. L. *Synthesis* **1986**, 496.

(18) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. A.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332.

(19) Prepared according to the general method described in: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(20) In most coupling experiments a number of different coupling conditions were examined to find the optimum reaction conditions; only the optimum conditions are reported. A range of palladium catalysts (e.g., Pd(PPh₃)₄, PdCl₂(PPh₃)₂, Pd₂(dba)₃), solvents (DMF, CH₃CN, and THF), additives (e.g., AsPh₃, P(*o*-tol)₃), and reaction temperatures were examined.

(21) A significantly higher yield was realized using 1-(benzenesulfonyl)-4-iodoimidazole.

(22) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1988**, 312.

(23) In model studies, 2-(tributylstannyl)phenylacetylene gave a better coupling yield with **3a** than phenylacetylene itself.

(24) Marvell, E. N.; Thomas, L. *Synthesis* **1973**, 457.

* Reaction conditions: (a) 5% Pd(PPh₃)₄, 10% CuI, Et₃N, DMF, 70 °C for **10** (40% yield); (b) 10% Pd(PPh₃)₄, DMF, 80 °C, for **16** (59% yield); (c) (1) *n*-BuLi, THF, -78 °C; (2) MeCONMe(OMe) (48%); (d) Lindlar reduction, (83%).

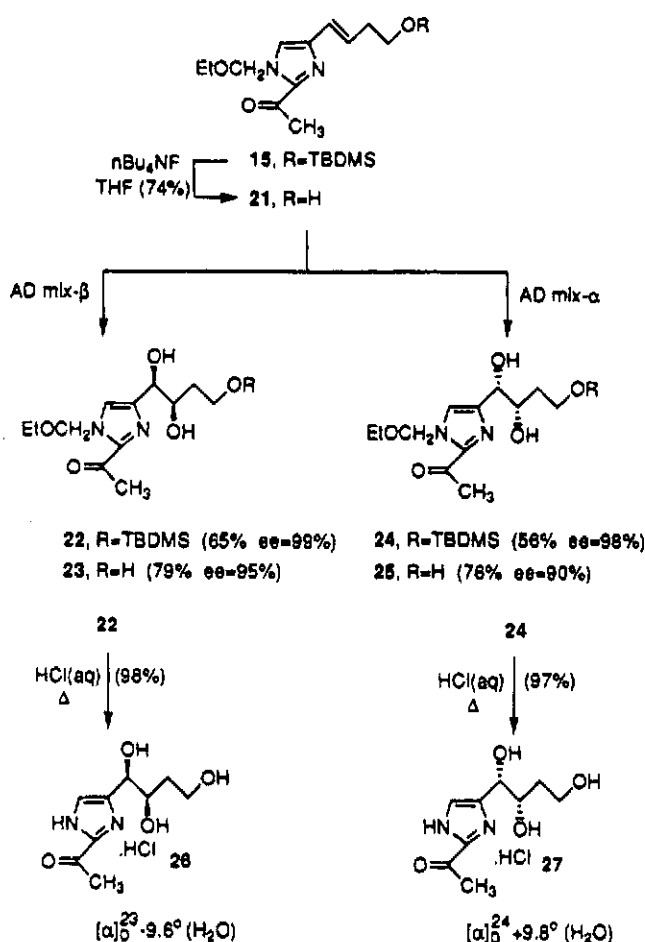
commercially available AD mix- α or AD mix- β ^{25,26} gave the syn-1,2-diols (1'*S*,2'*S*)-**24** or (1'*R*,2'*R*)-**22**, respectively, in moderate yields. The enantiomeric purities of **22** and **24** were 99 and 98%, respectively, as determined by ¹H NMR analysis of their Mosher diesters.²⁷ Catalytic AD of the alcohol **21** with AD mix- β or AD mix- α gave triols **23** or **25**, respectively, in good yield but in poorer enantiomeric purities as determined by ¹H NMR analysis of their respective tri-Mosher esters (Scheme 5). Hy-

(25) ADMix- α and ADMix- β were purchased from the Aldrich Chemical Co.

(26) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Harting, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme 5



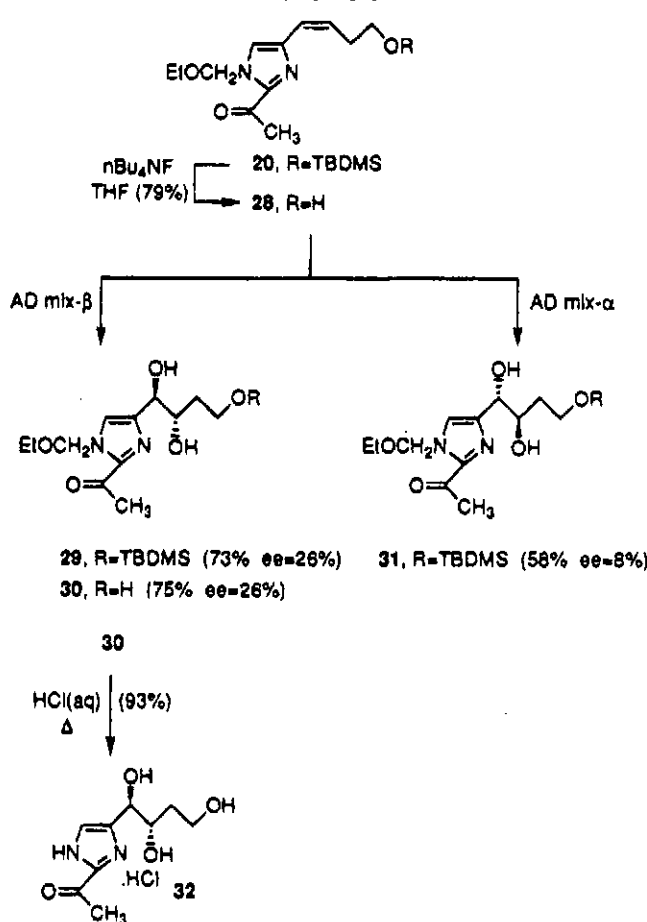
hydrolysis of **22** and **24** with aqueous hydrochloric acid at reflux for 1 h gave the imidazole hydrochloride salts **26** and **27**, respectively, in excellent yields (Scheme 5). The optical rotations of **26** and **27** were essentially equal and opposite in magnitude.

In contrast to the (*E*)-alkene **15**, the catalytic AD of the (*Z*)-alkene **20** gave the *anti*-1,2-diols **29** and **31** with poor enantiomeric purities (Scheme 6). While the AD of (*Z*)-alkenes is known to give 1,2-diols in lower enantiomeric purities than their isomeric (*E*)-alkenes,²⁸ it has been reported that higher enantiomeric purities can be realized from (*Z*)-allylic alcohols and (*Z*)-homoallylic alcohols.²⁹ It has been suggested that hydrogen bonding between the hydroxy group and an oxo group on the osmium is responsible for the higher enantiotropic π -face selectivity in these substrates. However, the AD of homoallylic alcohol **28** gave the 1,2,4-triol **30** in the same enantiomeric purity as that of **29** obtained from the AD of **20**. Acid-catalyzed hydrolysis of **30** gave the imidazole hydrochloride salt **32** in 93% yield. The stereochemical assignments to the products from the AD reactions were based upon Sharpless's mnemonic^{26,28} and were supported by ¹H NMR analysis of their Mosher esters.³⁰

Conclusion

In summary, we have developed a new and potentially general method for the synthesis of THI analogues from

Scheme 6



1-(ethoxymethyl)-4-iodoimidazole (**3a**) using palladium(0)-catalyzed coupling reactions with vinylstannanes, alkynes, and 1-(trimethylstannyl)alkynes to prepare 4-alkenyl- and 4-alkynylimidazoles. These methods should be generally useful for preparing other 4-substituted and 2,4-disubstituted imidazoles.³¹ The 1-(ethoxymethyl) protecting group allowed regioselective functionalization of the C-2 imidazole position. The catalytic AD was employed to introduce the 1,2-dihydroxy functionality of THI analogues. However, only the (*E*)-alkenes **15** and **21** gave 1,2-diols in high enantiomeric purities. The biological activity of the triols **26**, **27**, and **32** is currently under investigation and will be reported elsewhere.

Experimental Section

All ¹H NMR and ¹³C NMR spectra were measured at 400 and 100 MHz, respectively, in CDCl₃ solution unless otherwise stated. All organic extracts were dried over MgSO₄. Column chromatography was performed on silica gel (70–230 mesh).

1-(Ethoxymethyl)-4(5)-iodoimidazole (3a) and (6). To a solution of 4-iodoimidazole (4.00 g, 20.6 mmol) in DMSO (20 mL) was added NaH (0.540 g, 22.7 mmol), and the solution was stirred at 80 °C under N₂ for 2 h. Chloromethyl ethyl ether (2.34 g, 24.7 mmol) in DMSO (4 mL) was added, and the solution was stirred for a further 2 h at 80 °C. The reaction mixture was then cooled to rt, poured into a 5% aqueous

(28) Sharpless, K. B.; Wang, L. J. Am. Chem. Soc. 1992, 114, 7568.

(29) Sharpless, K. B.; Van Nieuwenhze, M. S.; Tetrahedron Lett. 1994, 35, 843.

(30) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. J. Am. Chem. Soc. 1991, 113, 4092.

(31) The only other generally efficient method for the regioselective preparation of 4-substituted imidazoles employs Grignard and organolithium reagents; see: Turner, R. M.; Ley, S. V.; Lindell, S. D. Synlett 1993, 748; Ley, S. V.; Lindell, S. D.; Turner, R. M. J. Chem. Org. Chem. 1991, 66, 6739. Lipshutz, B. H.; Hagen, W. Tetrahedron Lett. 1992, 33, 5885. Groziak, M. P.; Wei, L. J. Org. Chem. 1991, 56, 4296. Katritzky, A. R.; Slawinski, J. J.; Brunner, F.; Gorun, S. J. Chem. Soc., Perkin Trans. 1 1989, 1139.

solution of NaHCO₃ (100 mL), and extracted with CH₂Cl₂ (4 × 100 mL). The combined extracts were dried and concentrated to leave a black oil which was purified by short path column chromatography (ethyl acetate/hexane 3/7) to give a mixture of **3a** and **6** as a light yellow oil (2.70 g, 52%). The ratio of **3a** to **6** was 91:9 as determined by ¹H NMR. The two isomers could be separated by careful column chromatography. **3a**: ¹H NMR δ 7.49 (1H, d, *J* = 1.2 Hz), 7.14 (1H, d, *J* = 1.2 Hz), 5.24 (2H, s), 3.45 (2H, q, *J* = 7.2 Hz), 1.19 (3H, t, *J* = 6.8 Hz); ¹³C NMR δ 138.6, 124.3, 82.6, 76.2, 64.5, 14.6. MS (ES + ve) *m/z* 253 (M + H⁺, 100), 59 (8); HRMS calcd for C₈H₉IN₂O 251.9760, found 251.9757. **6**: ¹H NMR δ 7.75 (1H, s), 7.15 (1H, s), 5.28 (2H, s), 3.49 (2H, q, *J* = 7.2 Hz), 1.20 (3H, t, *J* = 6.8 Hz); ¹³C NMR δ 140.1, 137.3, 76.3, 69.4, 64.2, 14.6; MS (ES + ve) *m/z* 253 (M + H⁺, 100), 59 (8).

4-Iodo-1-*p*-tosylimidazole (3b). To a stirred solution of 4-iodoimidazole⁸ (2.00 g, 10.3 mmol) and *p*-toluenesulfonyl chloride (1.97 g, 10.3 mmol) in dry THF (40 mL) under N₂ was added triethylamine (1.04 g, 10.3 mmol) and the solution left to stir for 24 h. The mixture was filtered, and the filtrate was diluted with CH₂Cl₂ (50 mL), washed with water (20 mL), dried, and evaporated. The resulting solid was recrystallized from ethanol to give **3b** as a white solid (2.80 g, 78%); mp 146–147 °C; ¹H NMR δ 7.88 (1H, d, *J* = 1.2 Hz), 7.83 (2H, d, *J* = 8.4 Hz), 7.78 (2H, d, *J* = 8.4 Hz), 7.37 (1H, d, *J* = 1.2 Hz), 2.46 (3H, s); ¹³C NMR δ 146.8, 137.6, 134.2, 130.6, 127.5, 122.3, 85.2, 21.8; MS (ES + ve) *m/z* 349 (M + H⁺, 100), 278 (52), 155 (22). Anal. Calcd for C₁₀H₉IN₂O₂S: C, 34.50; H, 2.61; N, 8.05. Found: C, 34.95; H, 2.63; N, 8.00.

1,1'-Di-*p*-tosyl-4,4'-biimidazole (9a). In a thick-walled tube was combined 4-iodo-1-tosylimidazole (0.400 g, 1.15 mmol), triethylamine (0.174 g, 1.72 mmol), alkene **7** (0.430 g, 2.30 mmol), and Pd(Ph₃P)₄ (53 mg). The reagents were dissolved in dry acetonitrile (4 mL), and the tube was flushed with a stream of nitrogen, sealed, and stirred at 100 °C for 18 h. The solution was filtered, and the filtrate was washed with a 5% aqueous solution of NaHCO₃, dried, and concentrated to leave a black solid, which was purified by column chromatography (ethyl acetate/hexane: 45/55) and combined with the solids collected to give **9a** as a cream solid (140 mg, 55%), mp 219–220 °C dec. An analytical sample was recrystallized from ethanol: ¹H NMR δ 7.97 (1H, d, *J* = 1.2 Hz), 7.82 (2H, d, *J* = 8.8 Hz), 7.60 (1H, d, *J* = 1.2 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 2.42 (3H, s); ¹³C NMR δ 146.4, 138.1, 136.7, 134.7, 130.4, 127.5, 113.4, 21.7; MS (ES + ve) *m/z* 443 (M + H⁺, 100), 279 (27), 102 (57). Anal. Calcd for C₂₀H₁₈N₄O₄S₂: C, 54.29; H, 4.10; N, 12.66. Found: C, 54.00; H, 4.11; N, 12.51.

1,1'-Ditrityl-4,4'-biimidazole (9b). In a thick-walled tube was combined 4-iodo-1-tritylimidazole⁸ (1.02 g, 2.30 mmol), alkene **7** (860 mg, 4.60 mmol), triethylamine (4.60 mmol), and Pd(Ph₃P)₄ (100 mg). Dry DMF (5 mL) was added, the tube was flushed with N₂ and sealed, and the contents were stirred at 100 °C for 24 h. The mixture was filtered, and the filtrate was added to a 5% aqueous solution of NaHCO₃ (10 mL) and refiltered. The combined solids were washed with water and then acetone to give a cream solid which was recrystallized from CHCl₃/toluene (1/1) to give **9b** as a white solid (0.52 g, 73%), mp 279–280 °C dec. Extraction of the aqueous phase with CH₂Cl₂ gave no identifiable olefinated product **8**: ¹H NMR δ 7.36 (1H, d, *J* = 1.6 Hz), 7.32–7.29 (9H, m), 7.28 (1H, d, *J* = 1.6 Hz), 7.19–7.17 (6H, m); ¹³C NMR (22.5 MHz, CDCl₃, in part) δ 142.7, 138.9, 136.7, 129.9, 128.0, 127.9, 117.1; MS (ES + ve) *m/z* 619.0 (M + H⁺, 61), 241 (100); HRMS calcd for C₄₄H₃₄N₄ 618.2783, found 618.2778.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-(tributylstannyl)-*trans*-1-butene (11). A mixture of the alkyne **10** (2.20 g, 12.0 mmol) and a catalytic amount of AIBN under N₂ was stirred at 80 °C. Tributyltin hydride (3.16 g, 10.9 mmol) was added, and the reaction was stirred at 80 °C for 3 h. The mixture was cooled to rt, and excess **10** was removed under high vacuum to give a quantitative yield (5.17 g) of a mixture of the stannanes **11** and **12** as a clear oil (11:12 = 81:19). No attempts were made to separate this mixture which was used in the next step without further purification. **11**: ¹H NMR δ 5.97–5.95 (2H, m, *J*_{Sn,H} = 77.6 Hz), 3.67 (2H, t, *J* = 6.8 Hz), 2.36 (2H, ddt, *J* = 2.0, 3.2, 6.8 Hz), 1.52–1.25 (18H, m), 0.90–

0.85 (18H, m). **12**: ¹H NMR δ 6.51 (1H, dt, *J* = 6.8, 12.8 Hz), 5.89 (1H, dt, *J* = 1.2, 12.4 Hz), 3.64 (2H, t, *J* = 7.2 Hz), 2.27 (2H, dq, *J* = 1.2, 6.8 Hz), 1.52–1.25 (18H, m), 0.90–0.85 (18H, m), 0.06 (6H, s).

4-[(*tert*-Butyldimethylsilyl)oxy]-*trans*-1-butenyl]-1-(ethoxymethyl)imidazole (14). A mixture of iodoimidazole **3a** (2.63 g, 10.4 mmol), vinylstannanes **11** and **12** (5.17 g, 10.9 mmol, 81:19 *trans*/*cis* isomers), and PdCl₂(Ph₃P)₂ (370 mg) in a thick-walled tube was dissolved in dry DMF (30 mL). The vessel was flushed with argon and sealed and then stirred in the dark at 80 °C for 24 h. The mixture was then cooled and diluted with ethyl acetate (200 mL). The solution was washed with a half-saturated aqueous solution of NaCl (3 × 80 mL), dried, and concentrated to leave a dark oil. Purification by column chromatography (ethyl acetate/hexane: 4/6) gave pure *cis*-**13** (0.145 g, 5%) and pure *trans*-**14** (1.64 g, 51%) as yellow oils. **13**: ¹H NMR δ 7.56 (1H, s), 7.06 (1H, s), 6.38 (1H, dt, *J* = 1.6, 11.6 Hz), 5.64 (1H, dt, *J* = 7.2, 12.0 Hz), 5.26 (2H, s), 3.76 (2H, t, *J* = 6.8 Hz), 3.46 (2H, q, *J* = 7.2 Hz), 2.67 (2H, dq, *J* = 1.6, 6.8 Hz), 1.19 (3H, t, *J* = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ¹³C NMR δ 140.4, 136.6, 127.1, 122.5, 117.2, 76.2, 64.3, 62.6, 32.9, 25.9, 18.3, 14.7, -5.3; MS (CI + ve) *m/z* 311 (M + H⁺, 48), 295 (11), 253 (100), 197 (71), 179 (38), 166 (46). **14**: ¹H NMR δ 7.51 (1H, d, *J* = 1.2 Hz), 6.90 (1H, d, *J* = 1.6 Hz), 6.33–6.31 (2H, m), 5.22 (2H, s), 3.71 (2H, t, *J* = 7.2 Hz), 3.43 (2H, q, *J* = 6.8 Hz), 2.42–2.37 (2H, m), 1.18 (3H, t, *J* = 6.8 Hz), 0.90 (9H, s), 0.06 (6H, s); ¹³C NMR δ 141.1, 137.1, 126.1, 123.0, 115.1, 76.2, 64.2, 63.0, 36.5, 25.9, 18.3, 14.6, -5.3; MS (ES + ve) *m/z* 311 (M + H⁺, 100), 288 (14); HRMS calcd for C₁₆H₃₀N₂O₂Si 310.2076, found 310.2091.

2-Acetyl-4-[(*tert*-butyldimethylsilyl)oxy]-*trans*-1-butenyl]-1-(ethoxymethyl)imidazole (15). Alkene **14** (2.00 g, 6.45 mmol) was dissolved in dry THF (10 mL) and set to stir under N₂ at -78 °C. *n*-BuLi (7.74 mmol) in hexanes was added, and the black solution was stirred for 1 h at -78 °C. Freshly distilled *N*-methoxy-*N*-methylacetamide¹⁹ (930 mg, 9.03 mmol) in dry THF (5 mL) was then added slowly, and the resulting solution was stirred for 1 h at -78 °C and for a further 1 h at rt. The mixture was diluted with CH₂Cl₂ (40 mL), washed with a 5% aqueous solution of NaHCO₃ (15 mL), dried, and concentrated to give a black oil. Purification of this oil by column chromatography (ethyl acetate/hexane: 4/6) gave **15** as a tan oil (1.43 g, 63%, 80% based on recovered alkene **14**) and starting alkene **14** (0.42 g); ¹H NMR δ 7.19 (1H, s), 6.44–6.33 (2H, m), 5.75 (2H, s), 3.74 (2H, t, *J* = 7.2 Hz), 3.53 (2H, q, *J* = 6.8 Hz), 2.67 (3H, s), 2.46–2.41 (2H, m), 1.19 (3H, t, *J* = 7.2 Hz), 0.91 (9H, s), 0.07 (6H, s); ¹³C NMR δ 190.0, 142.3, 140.7, 128.1, 122.7, 120.9, 77.0 (EtOCH₂, over CDCl₃), 64.8, 62.8, 36.4, 27.3, 25.9, 18.3, 14.8, -5.3; MS (CI + ve) 353 (M + H⁺, 13), 337 (6), 307 (15), 295 (65), 207 (22); HRMS calcd for C₁₈H₃₂N₂O₃Si 353.2182, found 352.2177.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-(trimethylstannyl)-1-butyne (16). Butyne **10** (3.00 g, 16.30 mmol) was dissolved in dry THF (10 mL), cooled to -78 °C, and set stirring under N₂. *n*-BuLi in hexanes (17.93 mmol) was then added, and the reaction was stirred for 10 min at -78 °C and 20 min at 0 °C. Trimethyltin chloride (3.40 g, 19.56 mmol) in THF (5 mL) was then added dropwise with LiCl precipitating out immediately. The mixture was then left to stir at 0 °C for 30 min and overnight at rt. The mixture was diluted with CH₂Cl₂ (40 mL) and washed with H₂O (15 mL) and then a saturated aqueous solution of NaCl (15 mL). The solution was dried and the solvent removed to leave a light yellow oil. Short path distillation (65 °C/0.5 mmHg) gave stannane **16** as a clear oil (4.84 g, 86%); ¹H NMR δ 3.72 (2H, t, *J* = 7.2 Hz), 2.45 (2H, t, *J* = 7.2 Hz), 0.893 (9H, s), 0.26 (9H, s, ²*J*_{119Sn,H} = 60.4 Hz, ²*J*_{117Sn,H} = 58.0 Hz), 0.07 (6H, s); HRMS calcd for C₁₃H₂₉Si¹²⁰SnO 349.1011, found 349.1011.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-butenyl]-1-(ethoxymethyl)imidazole (17). Method **a**. A mixture of iodoimidazole **3a** (0.500 g, 1.98 mmol), alkyne **10** (0.550 g, 2.98 mmol), triethylamine (2.00 g, 19.8 mmol), CuI (40 mg), and PdCl₂(Ph₃P)₂ (70 mg) were dissolved in dry acetonitrile (10 mL). The solution was degassed with argon and heated to reflux under N₂ for 3 h. The solution was cooled to rt, poured

into H₂O (80 mL), and extracted with CH₂Cl₂ (3 × 100 mL), and the extracts were dried. The solvent was removed to leave a red oil which was purified by column chromatography (ethyl acetate/hexane: 55/45) to give pure **17** (242 mg, 40% based on **3a**) and 1,8-bis[(*tert*-butyldimethylsilyloxy)-3,5-octadiyne (**18**) as a dark oil (380 mg, 35% from **10**).

Method b. Into a thick-walled tube was added iodoimide **3a** (0.50 g, 1.98 mmol), stannane **16** (1.03 g, 2.97 mmol), and Pd(PPh₃)₄ (229 mg). The reagents were dissolved in dry DMF (8 mL), and the vessel was flushed with argon, sealed, and left to stir for 24 h at 80 °C. The dark mixture was then diluted with ethyl acetate (40 mL), filtered, washed with H₂O (2 × 15 mL), dried, and concentrated to give a dark oil. Purification by column chromatography (ethyl acetate/hexane: 1/1) gave **17** (360 mg, 59%): ¹H NMR δ 7.50 (1H, d, *J* = 1.2 Hz), 7.13 (1H, d, *J* = 1.2 Hz), 5.23 (2H, s), 3.81 (2H, t, *J* = 7.6 Hz), 3.43 (2H, q, *J* = 7.2 Hz), 2.62 (2H, t, *J* = 7.6 Hz), 1.18 (3H, t, *J* = 6.8 Hz), 0.90 (9H, s), 0.08 (6H, s); ¹³C NMR (22.5 MHz, CDCl₃) δ 136.9, 125.5, 121.6, 86.9, 76.3, 74.8, 64.6, 61.8, 25.8, 23.7, 18.2, 14.5, -5.4; MS (ES + ve) *m/z* 309 (M + H⁺, 100); HRMS calcd for C₁₅H₂₈N₂O₂Si (M⁺ - Me) 293.1685, found 293.1676.

1,8-Bis[(*tert*-butyldimethylsilyloxy)-3,5-octadiyne (18**).** An analytical sample of **18** was obtained as a pale oil after distillation (Kugelrohr, 117 °C/0.5 mmHg): ¹H NMR δ 3.72 (4H, t, *J* = 7.2 Hz), 2.46 (4H, t, *J* = 7.2 Hz), 0.89 (18H, s), 0.07 (12H, s); ¹³C NMR δ 74.5, 66.3, 61.5, 25.8, 23.6, 18.3, -5.4; MS (ES + ve) *m/z* 367 (M + H⁺, 100), 309 (74); HRMS calcd for C₁₈H₃₄O₂Si₂ 351.2175, found 351.2174.

2-Acetyl-4-[4-[(*tert*-butyldimethylsilyloxy)-1-butynyl]-1-(ethoxymethyl)imidazole (19**).** Imidazole **17** (400 mg, 1.30 mmol) was dissolved in dry THF (4 mL) and was stirred under N₂ at -78 °C. *n*-BuLi in hexanes (2.73 mmol) was added, and the reaction was stirred for 1 h at -78 °C before *N*-dimethoxy-*N*-methylacetamide (0.350 g, 3.25 mmol) was added dropwise in THF (5 mL). The mixture was then stirred for 1 h at -78 °C and a further 1 h at rt before being diluted with CH₂Cl₂ (15 mL). The solution was washed with a 5% aqueous solution of NaHCO₃ (6 mL), and the dark solution was dried. The solvent was removed, and purification by column chromatography (ethyl acetate/hexane: 1/9) gave **19** (220 mg, 48%) as a tan oil: ¹H NMR δ 7.35 (1H, s), 5.75 (2H, s), 3.82 (2H, t, *J* = 7.2 Hz), 3.53 (2H, q, *J* = 7.2 Hz), 2.67 (3H, s), 2.64 (2H, t, *J* = 7.2 Hz), 1.20 (3H, t, *J* = 7.2 Hz), 0.91 (9H, s), 0.09 (6H, s); ¹³C NMR δ 190.4, 141.9, 127.0, 124.9, 87.8, 77.3, 73.9, 65.0, 61.5, 27.3, 25.8, 23.6, 18.2, 14.7, -5.4; MS (ES + ve) *m/z* 351 (M + H⁺, 100), 317 (6), 289 (16); IR (neat) 2247, 1683 cm⁻¹; HRMS calcd for C₁₇H₂₈N₂O₃Si 335.1791, found 335.1758.

2-Acetyl-4-[4-[(*tert*-butyldimethylsilyloxy)-*cis*-1-butenyl]-1-(ethoxymethyl)imidazole (20**).** A solution of acetyl-imidazole **19** (1.00 g, 2.86 mmol), quinoline (370 mg, 2.86 mmol), and 10% Pd/CaCO₃ (160 mg) in ethyl acetate/hexane (15 mL, 1:1) was stirred under a H₂ atmosphere (1 atm) for 90 min. The mixture was then filtered and concentrated in vacuo, and the crude product was purified by column chromatography (ethyl acetate/hexane: 2/98) to give the *cis*-alkene **20** (840 mg, 83%): ¹H NMR δ 7.30 (1H, s), 6.37 (1H, dt, *J* = 11.6, 1.6 Hz), 5.77 (2H, s), 5.75 (1H, dt, *J* = 11.6, 7.2 Hz), 3.77 (2H, t, *J* = 6.8 Hz), 3.54 (2H, q, *J* = 6.8 Hz), 2.73 (2H, dq, *J* = 2.0, 6.8 Hz), 2.67 (3H, s), 1.20 (3H, t, *J* = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ¹³C NMR δ 191.0, 142.0, 139.9, 129.4, 123.4, 121.7, 77.0, 64.9, 62.6, 32.9, 27.4, 25.9, 18.3, 14.9, -5.3; MS (ES + ve) *m/z* 363 (M + H⁺, 100), 316 (20), 288 (65); IR (neat) 1680 cm⁻¹; HRMS calcd for C₁₇H₂₈N₂O₃Si (M⁺ - Me) 337.1947, found 337.1933.

2-Acetyl-4-(4-hydroxy-*trans*-1-butenyl)-1-(ethoxymethyl)imidazole (21**).** Silyl ether **15** (700 mg, 1.99 mmol) and Bu₄NF (1.04 g, 3.98 mmol) were dissolved in THF (10 mL), and the solution was stirred at rt for 75 min. The dark solution was then diluted with ethyl acetate (30 mL) and washed consecutively with a saturated aqueous solution of NaCl (10 mL) and H₂O (10 mL). The aqueous washings were extracted with ethyl acetate (2 × 20 mL), and the combined extracts were dried and concentrated to leave a thick dark oil. Purification by column chromatography (ethyl acetate/hex-

ane: 1/1) gave a light yellow oil which solidified on standing (350 mg, 74%): mp 80–81 °C; ¹H NMR δ 7.20 (1H, s), 6.43–6.41 (2H, m), 5.75 (2H, s), 3.80–3.75 (2H, m), 3.53 (2H, q, *J* = 7.2 Hz), 2.68 (3H, s), 2.51–2.67 (2H, m), 1.69 (1H, t, *J* = 5.6 Hz), 1.19 (3H, t, *J* = 7.2 Hz); ¹³C NMR δ 191.0, 142.3, 140.4, 127.6, 123.7, 121.3, 77.1, 64.9, 61.8, 36.2, 27.4, 14.8. MS (ES + ve) *m/z* 239 (M + H, 100), 197 (15). Anal. Calcd for C₁₂H₁₈N₂O₃: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.66; H, 7.82; N, 11.58.

(1R,2R)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsilyloxy)butyl]-1-(ethoxymethyl)imidazole (22**). Representative AD Procedure.** To a stirred solution of AD mix-β (1.80 g) and (DHQD)₂PHAL (40 mg) in H₂O (6.5 mL) and *t*-BuOH (3 mL) at rt was added methanesulfonamide (244 mg, 2.56 mmol). The two-phase system was then cooled to 0 °C, and the *trans*-alkene **21** (400 mg, 1.14 mmol) in *t*-BuOH (3.5 mL) was added in one addition. The system was left to stir at 0 °C for 3 d. Na₂SO₃ (1.8 g) was then added at 0 °C, and the mixture was warmed to rt and left to stir for 1 h. H₂O (2 mL) was added, the mixture was extracted with CH₂Cl₂ (4 × 10 mL) and dried, and the solvent was removed to leave a yellow oil. Purification by column chromatography (ethyl acetate/hexane: 4/6) gave a thick yellow syrup (285 mg, 65%): [α]_D²⁵ -13.7° (c 2.85, CHCl₃); ee = 99%; ¹H NMR δ 7.33 (1H, s), 5.75 (2H, ABq, *J* = 10.8 Hz), 4.61 (1H, dd, *J* = 4.0, 5.6 Hz), 4.16 (1H, dt, *J* = 4.0, 7.2 Hz), 4.01 (1H, d, *J* = 3.2 Hz), 3.91–3.88 (2H, m), 3.55 (2H, q, *J* = 6.8 Hz), 3.50 (1H, d, *J* = 6.4 Hz), 2.64 (3H, d, *J* = 0.4 Hz), 1.91–1.78 (2H, m), 1.20 (3H, t, *J* = 6.8 Hz), 0.91 (9H, s), 0.10, 0.09 (2 × 3H, 2 × s); ¹³C NMR δ 190.5, 143.3, 141.8, 122.2, 77.02, 73.0, 70.8, 64.9, 61.0, 35.0, 27.2, 25.7, 18.0, 14.7, -5.65, -5.67; MS (CI + ve) *m/z* 387 (M + H⁺, 100), 371 (12), 329 (10); HRMS calcd for C₁₈H₃₀N₂O₅Si 387.2315, found 387.2326.

(1R,2R)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (23**).** Using the general procedure described above for the synthesis of **22**, compound **23** was obtained as a white solid (79%), after purification by column chromatography (methanol/ethyl acetate: 1/9): mp 102–103 °C; [α]_D²⁵ -11.2° (c 1.35, MeOH); ee = 95%; ¹H NMR δ 7.31 (1H, s), 5.77, 5.74 (2H, ABq, *J* = 10.4 Hz), 4.54 (1H, dd, *J* = 4.0, 7.2 Hz), 4.21–4.16 (1H, m), 3.92–3.89 (2H, m), 3.92–3.89 (2H, m), 3.87 (1H, d, *J* = 2.8 Hz), 3.56 (2H, q, *J* = 6.8 Hz), 3.50 (1H, d, *J* = 5.2 Hz), 3.10–3.08 (1H, m), 2.64 (3H, s), 2.01–1.92 (1H, m), 1.84–1.77 (1H, m), 1.21 (3H, t, *J* = 6.8 Hz); ¹³C NMR (CD₃OD) δ 191.5, 144.8, 143.0, 124.7, 78.1, 72.7, 65.8, 60.0, 36.7, 27.4, 15.2; MS (CI + ve) *m/z* 256 (M⁺ - CH₃, 13), 237 (26), 209 (26), 97 (64), 139 (100). Anal. Calcd for C₁₂H₂₀N₂O₅: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.65; H, 7.53; N, 10.02.

(1S,2S)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsilyloxy)butyl]-1-(ethoxymethyl)imidazole (24**).** Using the general procedure described above for the synthesis of **22**, compound **24** was obtained as a thick yellow syrup (56%) after purification by column chromatography (ethyl acetate/hexane: 4/6): [α]_D²⁵ 13.3° (c 2.45, CHCl₃); ee = 98%. Spectral data were identical to **22**.

(1S,2S)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (25**).** Using the general procedure described above for the synthesis of **22**, compound **25** was obtained as a white solid (76%), mp 102–103 °C, after purification by column chromatography (methanol/ethyl acetate: 1/9): [α]_D²⁵ 11.7° (c 1.3, MeOH); ee = 90%. Spectral data were identical to **23**.

(1R,2R)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (26**). Representative Deprotection Procedure.** A solution of the silyl ether **22** (280 mg, 0.73 mmol) in ethanol/H₂O (1:1, 10 mL) and concd HCl (5 mL) was refluxed for 1 h and cooled to rt, and the ethanol removed in vacuo. The aqueous solution was washed with ether (3 × 5 mL) and concentrated to give the HCl salt **26** as a tan solid (180 mg, 98%): mp 236–242 °C dec; [α]_D²⁵ -9.6° (c 1.80, H₂O); ¹H NMR (D₂O) δ 7.48 (1H, s), 4.73 (1H, d, *J* = 4.4 Hz), 3.84 (1H, dd, *J* = 4.0, 14 Hz), 3.57–3.52 (2H, m), 2.53 (3H, s), 1.64–1.46 (2H, m); ¹³C NMR (D₂O, MeOH internal reference) δ 184.7, 139.4, 137.0, 119.3, 70.1, 68.8, 58.2, 34.2, 26.4; MS (ES + ve) *m/z*

215 ($C_9H_{15}N_2O_4^+$, 100), 197 (15); HRMS calcd for $C_9H_{15}N_2O_4$, 215.1032, found 215.1043.

(1S,2S)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (27). Using the general procedure described above for the synthesis of 26, compound 27 was obtained as a tan solid (97%), $[\alpha]_D^{24} +9.8^\circ$ (c 1.50, H_2O). Spectral data were identical to 26.

2-Acetyl-4-(4-hydroxy-*cis*-1-butenyl)-1-(ethoxymethyl)imidazole (28). Silyl ether 20 (0.750 g, 2.13 mmol) and Bu_4NF (1.11 g, 4.26 mmol) were dissolved in THF (10 mL) and stirred at rt for 75 min. The solution was diluted with ethyl acetate (30 mL) and washed consecutively with a saturated aqueous solution of NaCl (10 mL) and H_2O (10 mL). The aqueous phase was re-extracted with ethyl acetate (20 mL), and the combined extracts were dried and concentrated to leave a thick oil. Purification by column chromatography (ethyl acetate/hexane: 35/65) gave alcohol 28 as a yellow oil (400mg, 79%); ^1H NMR δ 7.24 (1H, s), 6.45 (1H, d, $J = 11.6$ Hz), 5.88–5.80 (1H, m), 5.77 (2H, s), 4.34 (1H, br s), 3.89–3.84 (2H, m), 3.56 (2H, q, $J = 7.2$ Hz), 2.81–2.75 (2H, m), 2.67 (3H, s), 1.21 (3H, t, $J = 7.2$ Hz); ^{13}C NMR δ 190.3, 141.3, 139.1, 129.9, 123.3, 121.8, 76.95, 64.9, 61.9, 31.8, 27.3, 14.6; MS (ES + ve) m/z 239 ($M + H^+$, 100), 197 (18), 102 (9), 59 (17); HRMS calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1315.

(1R,2S)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsiloxy)butyl]-1-(ethoxymethyl)imidazole (29). Using the general procedure described above for the synthesis of 22, compound 29 was obtained as a light yellow oil (73%) after purification by column chromatography (ethyl acetate/hexane: 35/65): ee = 26%; ^1H NMR δ 7.34 (1H, s), 5.75 (2H, s), 4.64 (1H, t, $J = 5.2$ Hz), 4.32 (1H, d, $J = 2.8$ Hz), 4.05–4.00 (1H, m), 3.94–3.84 (2H, m), 3.74 (1H, d, $J = 4.8$ Hz), 3.55 (2H, q, $J = 7.2$ Hz), 2.63 (3H, s), 1.86–1.81 (2H, m), 1.20 (3H, t, $J = 7.2$ Hz), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR δ 190.5, 143.4, 141.7, 122.2, 77.2, 74.4, 70.8, 65.0, 61.2, 34.6, 27.3, 25.8, 18.1, 14.8, –5.5; MS (ES + ve) m/z 387 ($M + H^+$, 100), 332 (7); HRMS calcd for $C_{18}H_{30}N_2O_5Si$ 387.2314, found 387.2307.

(1R,2S)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (30). Using the general procedure described above for the synthesis of 22, compound 30 was obtained as a white solid (75%), after purification by column chromatography (methanol/ethyl acetate: 1/9); mp 83–84 $^\circ C$; ee = 26%; ^1H NMR δ 7.34 (1H, s), 5.76 (2H, s), 4.65 (1H, d, J

= 5.6 Hz), 4.12–4.04 (1H, m), 3.96–3.86 (2H, m), 3.56 (2H, q, $J = 7.2$ Hz), 2.64 (3H, s), 1.87–1.74 (2H, m), 1.21 (3H, t, $J = 7.2$ Hz); ^{13}C NMR δ 190.2, 142.8, 141.7, 122.6, 77.1, 73.5, 71.0, 65.1, 59.8, 34.0, 27.2, 14.7; MS (ES + ve) m/z 294 ($M + Na^+$, 100), 139 (100), 102 (65).

(1S,2R)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsilyloxy)butyl]-1-(ethoxymethyl)imidazole (31). Using the general procedure described above for the synthesis of 22, compound 31 was obtained as a thick pale oil (58%), after purification by column chromatography (ethyl acetate/hexane: 35/65), ee = 8%. Spectral data were identical to 29.

(1R,2S)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (32). Triol 30 (110mg, 0.40 mmol) was dissolved in ethanol/ H_2O (1:1, 8 mL) and concd HCl (4 mL), and the solution was heated to reflux for 1 h. The solvent was then removed and the sample dried under high vacuum at ca. 60 $^\circ C$ for 2 h to give a highly hygroscopic yellow glassy solid of the HCl salt 32 (94mg, 93%). An analytical sample was recrystallized from ethanol/acetonitrile: mp 129–131 $^\circ C$; ^1H NMR (D_2O/DCI) δ 7.56 (1H, s), 4.78 (1H, d, $J = 5.2$ Hz), 3.96 (1H, ddd, $J = 2.8, 5.6, 10.0$ Hz), 3.67–3.63 (2H, m), 2.63 (s, 3H), 1.82–1.70 (1H, m), 1.49–1.40 (1H, m); ^{13}C NMR (D_2O/DCI , MeOH reference) δ 185.2, 139.8, 136.7, 119.8, 70.4, 68.9, 58.2, 34.4, 26.3; MS (ES + ve) m/z 215 ($M + H^+$, 100), 197 (59), 179 (47). Anal. Calcd for $C_9H_{15}ClN_2O_4 \cdot 1/3H_2O$: C, 42.17; H, 6.15; N, 10.91. Found: C, 42.32; H, 6.18; N, 10.61.

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Supplementary Material Available: ^1H NMR of *N*-methyl-*N*-methoxyacetamide, 3b, 9b, 11 (and 12), 13–23, 29, 30, and 32. ^{13}C NMR of 5, 6, 9a, and 26 (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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PCT
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SOLICITUD DE:

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Capítulo I

☐

Capítulo II

2
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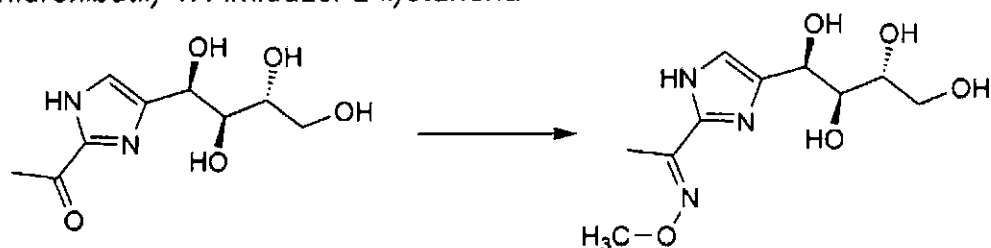
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solución de HCl en dioxano (4M, 60 ml). Después de algunos minutos, se observó un precipitado blanco, y se continuó la agitación durante un total de 30 minutos, antes de filtrarse a través de un filtro de vidrio fritado y enjuagar la torta de filtrado con dioxano y éter. La torta se redisolvió en agua (200 ml), se sonicó durante 5 min, luego se enfrió a 0°C, se trató con celite (5 g), y se filtró a través de un filtro de vidrio fritado. La solución acuosa se concentró a sequedad, luego se aisló desde metanol (30 ml) / dietiléter (60 ml) para dar la *E*-oxima como un polvo blanco analíticamente puro (3.8 g, 80% de rendimiento).

6.5. Síntesis de *O*-metiloxima de (Z)-1-(4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahidroxibutil)-1*H*-imidazol-2-il)etanona



El compuesto del título se preparó como se ha descrito en en Ejemplo 6.3, usando clorhidrato de metoxilamina en lugar de clorhidrato de hidroxilamina, con 74% de rendimiento. El producto se obtuvo como un sólido blanco liviano.

LCMS: Columna Sunfire C-18, 4.6 x 50mm; 0 – 17% MeOH (0.1% TFA) en agua (0.1% TFA) a lo largo de 5 min; velocidad de flujo = 3 ml/min; Detección 220 nm; Tiempos de retención : 1.59 minutos (isómero syn, 260.1 (M+1)) y 1.73 min (isómero anti, 260.1 (M+1)). ¹H NMR (D₂O) δ 2.18 y 2.22 (singuletes, 3H), 3.54 – 3.60 (m, 1H), 3.66 – 3.79 (m, 3H), 3.94 y 3.95 (singuletes, 3H), 4.76 (ancho, protones OH y H₂O), 4.93 y 4.97 (singuletes, 1H),

4C