SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Bogotá, D.C.,

Abogado
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ASUNTO

Radicación	11 029 749
Trámite	011
Evento	378
Actuación	519
Oficio	- 20122
Folios	15

Patente de Invención	☑		Patente de Modelo de Utilidad
Vía Nacional			
Vía PCT (Fase Nacional)	☑	Capítulo I	☑ Capítulo II
No. Solicitud Internacional		PCT/EP2009/006670	
Fecha de Presentación Internacional		15/Septiembre/2009	

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 9 a 144	10/Marzo/2011
Reivindicaciones:	Folios 145 a 149	10/Marzo/2011
Prioridad:	EP 080 162 36.5	15/Septiembre/2008
	US 61 096 964	15/Septiembre/2008

2. Análisis de la Prioridad

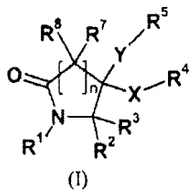
Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

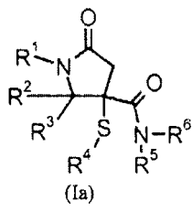
Título de la solicitud: "Pirrolidin-2-onas como ligandos de HDM2"

El problema planteado en esta solicitud consiste en proporcionar compuestos ligandos de unión a la proteína HDM2, que inducen la apoptosis y la inhibición de la proliferación y que son útiles en el tratamiento del cáncer e infecciones virales.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos de la fórmula (I) y (Ia) y composiciones que lo contienen.



(I)



(Ia)

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C 07 D 401/12, 401/14, 403/04, 403/14, 409/12, 409/14, 207/277, 401/06; A 61 K 31/4015; A 61 P 35/00, 31/00.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 15 y 16 no es patentable, de acuerdo con el Art 14.

La Reivindicación 16 a pesar de que se encabeza como un compuesto o composición farmacéutica, menciona el uso que puede dársele a dicho compuesto o dicha composición, por lo que se considera un uso.

5. De la Solicitud de Patente

Titulo

El título es muy general y no define el objeto de de la solicitud, por lo cual se sugiere al solicitante hacer la corrección necesaria.

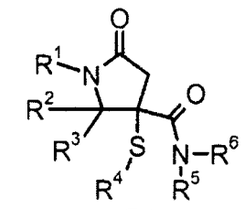
Reivindicaciones (Art 30 D 486, Art 22 PCT)

En la Reivindicación 1, si bien es cierto que para la persona del oficio versada en la materia los términos "solvatos" e "hidratos" son conocidos, no se evidencia en la descripción que éstos puedan llegar a formarse. Por lo tanto se sugiere eliminar los mencionados términos del alcance del capítulo reivindicatorio, porque no encuentran soporte en la descripción.

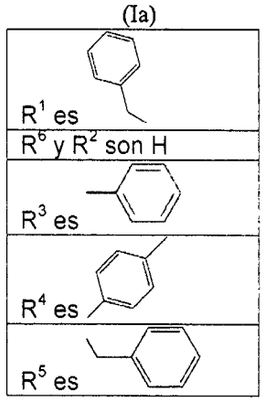
La Reivindicación 1 no es concisa, porque presenta una excesiva complejidad, lo cual dificulta determinar la extensión del objeto que se busca proteger. En particular, cuando menciona los términos: "alquilo", "heteroarilo", "arilo", "cicloalquilo", "alquenilo", "alquinilo", "heteroalquilo", "alquilcicloalquilo", "heteroalquilcicloalquilo", "aralquilo", "hetero-aralquilo", con los cuales se pueden presentar múltiples opciones de posibles compuestos, dificultando entender el alcance de la materia reclamada en la solicitud ya que no se especifica el número de átomos de carbono que los conforman o los heteroátomos que hacen parte de los heteroarilos, heterociclos y los que correspondan.

Por tal motivo se obtienen un número indefinido de compuestos que no encuentran soporte en la descripción.

Se sugiere al solicitante restringir la solicitud a una razonable generalización del tipo de compuestos que han sido sintetizados ó probados, es decir, que se encuentran debidamente sustentados en la descripción, por ejemplo como se observa a lo largo de las realizaciones preferidas mencionadas en los ejemplos del capítulo descriptivo y en las reivindicaciones cuando:



(Ia)



Lo anterior aplica también para las reivindicaciones dependientes a la Reivindicación 1 que emplean tales términos. Se sugiere realizar las aclaraciones necesarias.

6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la Solicitud de Prioridad: Septiembre 15 de 2008, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	Artículo [1]	Cycloaddition reactions of imines with 3-thiosuccinic anhydrides: Synthesis of the tricyclic core of martinellic acid	15/Junio/2006
D2	Artículo [2]	Diastereoselective synthesis of gamma-lactams by a one-pot, four-component reaction	06/Agosto/2007
D3	Artículo [3]	Antagonists as Anti-HIV agents. 1. Synthesis and Biological Evaluation of 5-Oxopyrrolidine-3-carboxamide Derivatives	24/Octubre/2003

D1: (folios 186 - 189), divulga reacciones de cicloadición de anhídridos succínicos ariltio-sustituidos con iminas para producir γ-lactamas con alto rendimiento y diasteroselectividad.

D2: (folios 190 - 193), divulga síntesis diasteroselectiva de γ-lactamas por reacción de cuatro compuestos en un paso, entre aminas, anhídridos maleicos, aldehídos y tioles.

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[1] **NG PUI YEE ET AL**: "Cycloaddition reactions of imines with 3-thiosuccinic anhydrides: Synthesis of the tricyclic core of martinellic acid" ORGANIC LETTERS, vol. 8, no. 18, August 2006 (2006-08), pages 3999-4002,

[2] **WEI JINGQIANG ET AL**: "Diastereoselective synthesis of gamma-lactams by a one-pot, four-component reaction." ORGANIC LETTERS 27 SEP 2007, vol. 9, no. 20, 27 September 2007 (2007-09-27), pages 4077-4080

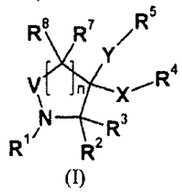
[3] **IMAMURA S ET AL**: "CCR5 Antagonists as Anti-HIV agents. 1. Synthesis and Biological Evaluation of 5-Oxopyrrolidine-3-carboxamide Derivatives" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 52, no. 1, 1 January 2004 (2004-01-01), pages 63-73,

D3: (folios 194 - 195), divulga antagonistas CCR5 como agentes anti-VIH-1, tal como el compuesto N-{3-[4-(4-fluorobenzoil)piperidin-1-il]propil}-1-metil-5-oxo-N-fenilpirrolidin-3-carboxamida.

7. **Examen de Patentabilidad** (Art 14 D486)

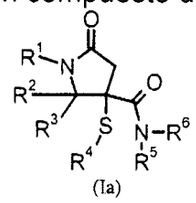
Novedad (Art 16 D486)

La Reivindicación 1 consiste en compuesto de fórmula (I):



(I)

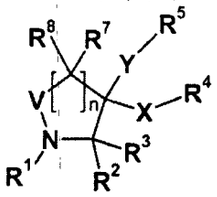
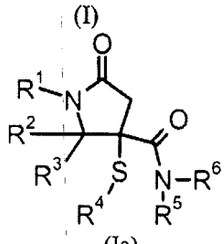
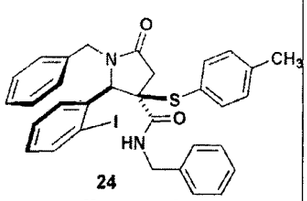
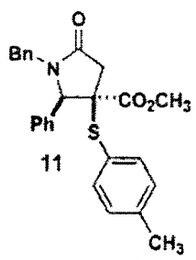
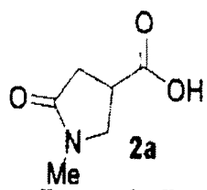
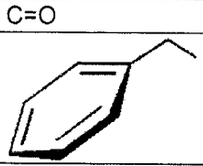
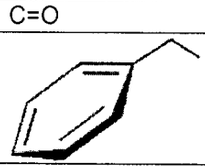
La Reivindicación 2 consiste en un compuesto de fórmula (Ia):

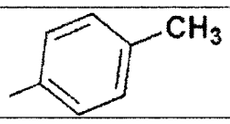
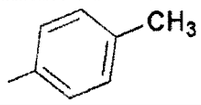
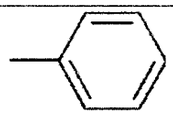


(Ia)

en donde R^1 – R^6 son como se encuentran definidos.

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

Características esenciales	**D1**	**D2**	**D3**
Compuesto de fórmula (I) y (Ia)  (I)  (Ia)	 24 [[comp. 24]] (folios 186 - 189, compuesto 24 y compuesto 27)	 [[comp. 11]] (Folios 190 - 193)	 2a [[comp. 2-a]] (ver folios 194 - 195)
V es C=O	C=O	C=O	C=O
R^1 es un radical alquilo, arilo o aralquilo			Me
R^3 es H o un arilo			H
R^2 es H	H	H	H
X es S o un enlace	S	S	enlace

R^4 es H o un arilo			H
Y es $CONR^6$ R^6 es H	CONH	COO	COO
R^5 es H, alquilo, aralquilo		CH_3	H
R^7 y R^8	H	H	H

Las características **esenciales** de los compuestos de las Reivindicaciones 1 y 2 habían sido divulgadas previamente en D1 – D3, que divulgan compuestos producto de reacciones de cicloadición de anhídridos succínicos ariltio-sustituidos con iminas para producir γ-lactamas con alto rendimiento y diasteroselectividad tal como las señaladas en los compuestos 24 y 27 (D1: ver folios 186 - 189), síntesis diasteroselectiva de γ-lactamas por reacción de cuatro compuestos en un paso, entre aminas, anhídridos maleicos, aldehídos y tioles (D2: ver folios 190 - 193) y antagonistas CCR5 como agentes anti-VIH-1, tal como el compuesto N-{3-[4-(4-fluorobenzoil)piperidin-1-il]propil}-1-metil-5-oxo-N-fenilpirrolidin-3-carboxamida (D3: ver folios 194 - 195)

En consecuencia, las Reivindicaciones 1 y 2 no son nuevas ó carecen de novedad, según lo divulgado en los documento D1.

Las reivindicaciones dependientes 2 – 14 no mencionan alguna característica que haga nuevos los compuestos de las Reivindicaciones 1 y 2, por lo cual se considera que no son nuevas.

8. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	**NG PUI YEE ET AL**	1 – 14	Novedad
D2	**WEI JINGQIANG ET AL**	1 – 14	Novedad
D3	**IMAMURA S ET AL**	1 – 14	Novedad

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 06 NOV. 2012

Elaborado por: Nelson Ricardo Velasco G
Revisado por: Jacqueline Alfonso Rozo

Expediente 11 029 749 1er Art 45

ORGANIC LETTERS
2006
Vol. 8, No. 18
3999–4002

186

D1

Cycloaddition Reactions of Imines with 3-Thiosuccinic Anhydrides: Synthesis of the Tricyclic Core of Martinellic Acid

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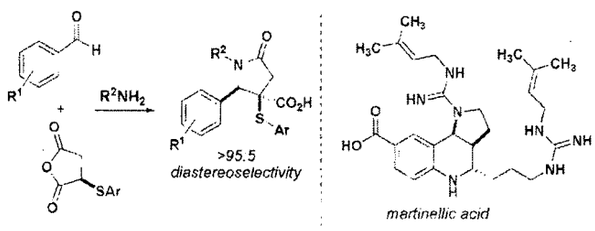
Received June 15, 2006

ABSTRACT



Arylthio-substituted succinic anhydrides undergo cycloaddition reactions with imines to produce γ-lactams in high yield and with high diastereoselectivity. The origin of the selectivity is proposed to result from anion–π repulsion in the transition state. The utility of this technique is demonstrated in a synthesis of the carbon framework common to the alkaloids martinellic acid and martinelline in five steps.

The diastereoselective synthesis of heterocyclic compounds is important for the discovery of biologically relevant compounds in drug discovery, chemical biology, and the synthesis of natural products.[1] γ-Lactams are an important class of unsaturated heterocycles featured in natural products and drug candidates.[2] The reaction of imines with succinic anhydrides represents an efficient, one-step synthesis of these compounds. The isolated[3] reports of lactam syntheses using this reaction suggest that the substrate scope is quite narrow (Figure 1, eqs 1 and 2). A recent report from our laboratory[4] details the importance of electronic factors on the reactivity of the anhydride component (Figure 1, eq 3). In this report, we exploit this effect to establish the reaction of imines with succinic anhydrides as a general method for γ-lactam synthesis.

Our observations on how substituent effects influence the rate of the reaction between aryl-substituted anhydrides and imines prompted us to examine heteroatom-substituted anhydrides. An inspection of substituted acetophenone acidity data[5] suggests that oxygen, nitrogen, and sulfur substituents confer various levels of stabilization to the conjugate base (Figure 2). On the basis of this trend, we hypothesized that heteroatom-substituted anhydrides would facilitate the imine–anhydride cycloaddition.

We tested this hypothesis by employing a series of heteroatom-substituted anhydrides[6] in addition reactions with imine **15**. Anhydrides **16**–**20** were allowed to react with the *N*-benzyl imine of *ortho*-bromobenzaldehyde (**15**) using conditions optimized for phenylsuccinic anhydride.[4] The reactions of nitrogen- and oxygen-substituted anhydrides

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(1) Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2125–2126 and references therein.

(2) (a) Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303. (b) Smith, M. B. *Sci. Synth.* **2005**, *21*, 647–711.

(3) (a) Castagnoli, N., Jr., *J. Org. Chem* **1969**, *34*, 3187–3189. (b) Castagnoli, N., Jr.; Cushman, M. *J. Org. Chem.* **1971**, *36*, 3404–3406. (c) Cushman, M.; Castagnoli, N., Jr., *J. Org. Chem.* **1972**, *37*, 1268–1271. (d) Dallacker, F.; Jouck, W. *Chem.-Ztg.* **1985**, *109*, 82–84. (e) Cushman, M.; Madaj, E. J. *J. Org. Chem.* **1987**, *52*, 907–915.

(4) Masse, C. E.; Ng, P. Y.; Fukase, Y.; Sanchez-Rosello, M.; Shaw, J. T. *J. Comb. Chem.* **2006**, *8*, 293–296.

(5) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (b) Bordwell, F. G.; Lynch, T. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558–7562.

10.1021/ol061473z CCC: $33.50
Published on Web 08/04/2006

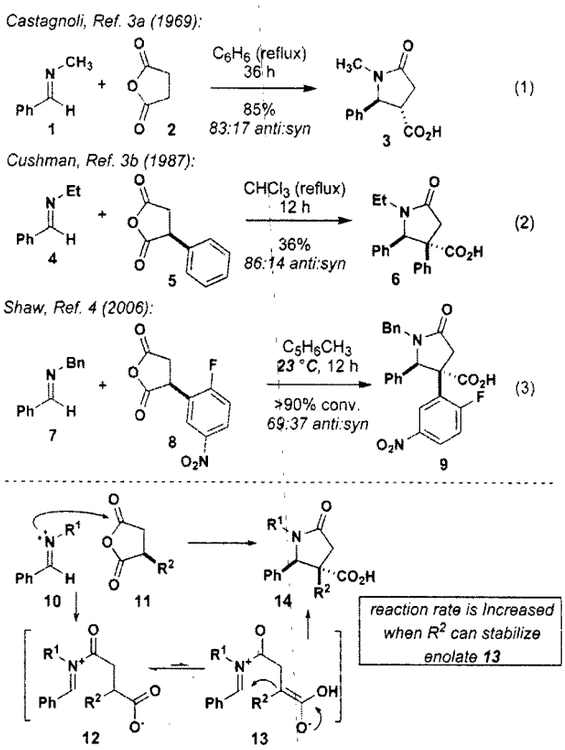
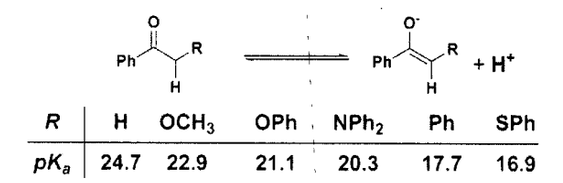


Figure 1. Reactions of imines with succinic anhydrides: increasing the enolate stabilization facilitates the reaction.

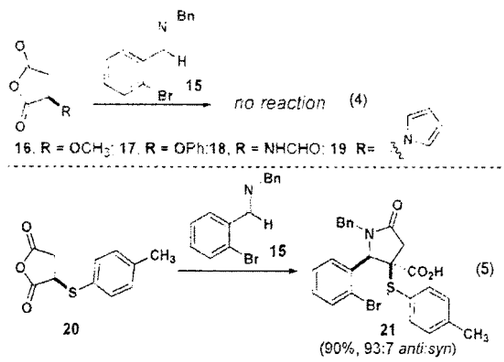


R	H	OCH_3	OPh	NPh_2	Ph	SPh
pK_a	24.7	22.9	21.1	20.3	17.7	16.9

Figure 2. Effect of heteroatom substitution on enolate stability.

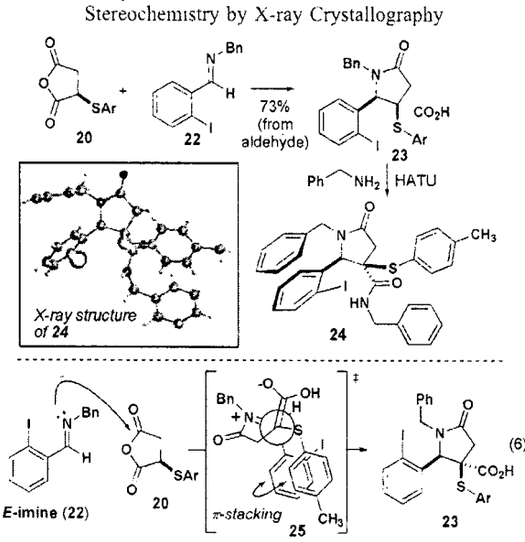
showed either no conversion or the formation of unidentified byproducts (eq 4). In contrast, sulfur-substituted anhydride **20** afforded the desired lactam product **21** in high yields and with the highest diastereoselectivity yet observed in this reaction (eq 5).

The reaction of imines with anhydride **20** preferentially leads to the anti diastereomer, as found with phenylsuccinic



anhydride. Iodo-substituted acid **23** was prepared in analogy to **21** and converted to amide **24**, which yielded a crystalline sample that was analyzed using X-ray crystallography (Scheme 1). The observed stereochemical outcome is consistent with a favorable π-stacking interaction in the transition state **25** between the two aromatic rings (eq 6).

Scheme 1. Synthesis of **24** and Establishment of the Relative Stereochemistry by X-ray Crystallography



The importance of π-stacking was evaluated by testing the reactivity of a thio*alkyl*-substituted succinic anhydride. *N*-Butylthio-substituted anhydride **26** was allowed to react with imine **15** under the standard conditions, and a nearly identical selectivity was observed for the anti diastereomer.[7] This result demonstrates that steric and/or electrostatic factors, rather than a π-stacking interaction, are mainly responsible for the selectivity observed in this reaction.

The observed selectivity in the reactions of thio-substituted anhydrides with imines can be rationalized by invoking a repulsive interaction between the negative charge of the

(6) Anhydride **18** was purchased from Sigma-Aldrich. Anhydrides **16**, **17**, **19**, and **20** were synthesized by reported methods, with minor modifications (see Supporting Information). **16**: (a) Barton, D. H. R.; Benechie, M.; Khuong-Huu, F., Potier, P.; Reyna-Pinedo, V. *Tetrahedron Lett.* **1982**, *23*, 651−654. **17**: (b) Sheppard, G. S. *Synlett* **1999**, 1207−1210. **19**: (c) Box, S. J.; Corbett, D. F. *Tetrahedron Lett.* **1981**, *22*, 3293−3296. (d) D'Silva, C.; Walker, D. A. *J. Org. Chem.* **1998**, *63*, 6715−6718. **20**: (e) Zienty, F. B.; Vineyard, B. D.; Schleppnik, A. A. *J. Org. Chem.* **1962**, *27*, 3140−3146.

(7) The relative configuration of this compound was proven by conversion to the *p*-methoxyphenethyl amide and NOE spectroscopy. See Supporting Information.

carboxylate and the aromatic ring of the imine in the transition state (Figure 3). Although the attractive interactions

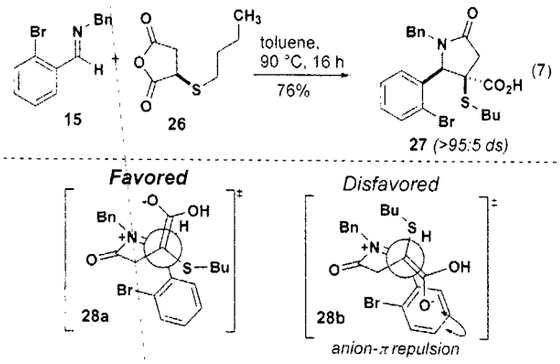


Figure 3. Reaction of **15** with thiobutyl succinic anhydride **26** (eq 7). The stereoselectivity is explained by anion-π repulsion in transition state **28b**.

of cations with π-systems have been extensively studied,[8] analogous studies of anion$-\pi$ interactions are less common. Deya has described the attraction of anions to electron-*deficient* arenes in detail.[9] This interaction has also been used to explain the bonding of aromatic heterocycles in macromolecular structures.[10] Although one would assume that the interaction of an anion with an electron-*rich* arene would be repulsive, this phenomenon has not been well-documented. One study of Lewis acids and bases interacting with arenes concludes that ammonia experiences an attractive interaction with hexafluoro-benzene and a repulsive interaction with the π-face of benzene (Figure 4).[11] Although the repulsion of the carboxylate and the aryl ring in the transition state of the imine−anhydride reaction (Figure 3) is consistent with the observed stereochemistry, further experimentation will bolster this argument.[12] To our knowledge, this is the first instance in which anion$-\pi$ repulsion has been invoked in a transition state to explain the stereochemical outcome of a reaction.

We explored the scope of this reaction with a variety of substituted imines (Table 1). Regardless of the N-substitution or the presence or absence of ortho substituents on the aromatic ring, good yields and excellent diastereoselectivities were observed for the reactions of imines with anhydride **20**.

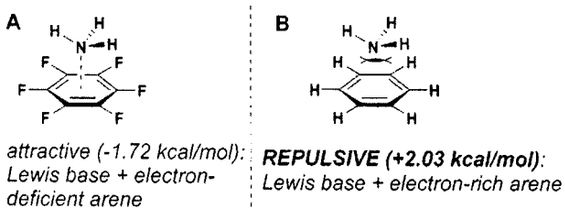
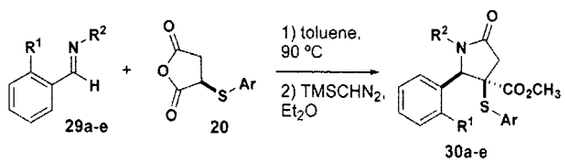


Figure 4. Interaction between a Lewis base (ammonia) which has been calculated to be attractive (**A**) when the arene is electron deficient and to be repulsive (**B**) when the arene is electron rich. Interaction energy calculated at the MP2/aug-ccpVDZ//B3LYP 6-311G(d) level.[11]

To demonstrate the utility of this technique, a cycloaddition/reduction sequence was used to prepare the tricyclic core shared by martinellic acid and martinelline in a short synthetic sequence. These two natural products were isolated

Table 1. Reaction of Anhydride **20** with Various Imines



entry	R^1	R^2	yield[a]	diastereoselectivity[b]
1	NO_2	Bn	80%	>95:5
2	N_3	Bn	85%	>95:5
3	H	$CH_2(^iPr)$	62%	>95:5
4	H	^{i}Pr	58%	>95:5
5	H	PMB[c]	76%	>95:5

[a] Yield over two steps from aldehyde starting material. [b] Determined by ^{1}H NMR spectroscopy. [c] PMB = *p*-methoxybenzyl.

from the tropical plant *Martinella iquitosensis*.[13] These two compounds share a common tricyclic core and their "deceptively simple"[14a] structures have attracted much synthetic effort.[14] Commercially available aldehyde **31** was treated with benzylamine, followed by anhydride **20**, to produce lactam

(8) Dougherty, D. A. *Science* **1996**, *271*, 163−168.

(9) (a) Quinonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389−3392. (b) Garau, C.; Quinonero, D.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *New J. Chem.* **2003**, *27*, 211−214. (c) Garau, C.; Frontera, A.; Quinonero, D.; Ballester, P.; Costa, A.; Deya, P. M. *Chem. Phys. Lett.* **2004**, *399*, 220−225.

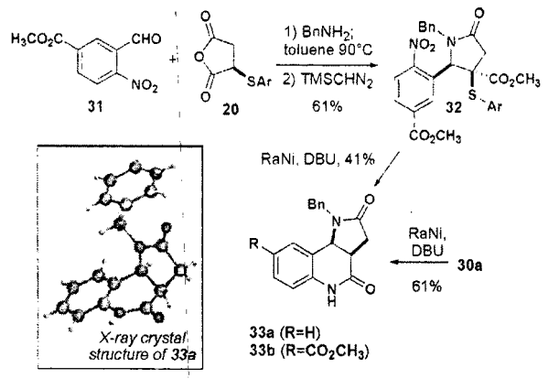
(10) (a) Schottel, B. L.; Chifotides, H. T.; Shatruk, M.; Chouai, A.; Perez, L. M.; Bacsa, J.; Dunbar, K. R. *J. Am. Chem. Soc.* **2006**, *128*, 5895−5912. (b) Kawahara, S.-i.; Tsuzuki, S.; Uchimaru, T. *Chem.−Eur. J.* **2005**, *11*, 4458−4464.

(11) We have attempted a reaction between the benzylimine of pentafluorobenzaldehyde and anhydride **20**, which was expected to give the lactam product with reduced diastereoselectivity. No conversion was observed, possibly due to reduced basicity of the imine nitrogen.

(13) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682−6685.

(14) Enantioselective synthesis of martinellic acid: (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189−2191. Syntheses of racemic martinellic acid and martinelline: (b) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217−4220. (c) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405−9409. (d) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916. Syntheses of the tricyclic core: (e) He, Y.; Mominga, R.; Lovely, C. J. *Tetrahedron Lett.* **2005**, *46*, 1251−1254. (f) Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481−3484. (g) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417−6419. (h) Hara, O.; Sugimoto, K.; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625−1627. (i) Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 9381−9390. (j) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977−3984.

Scheme 2. Imine–Anhydride Cycloaddition and Reductive Desulfurization/Cyclization



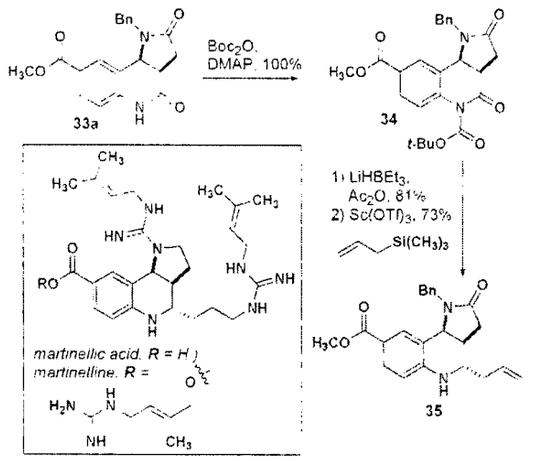
32 in 61% yield and >95:5 diastereoselectivity (Scheme 2). Treatment of this compound with Raney nickel effected reductive cleavage of the arylthio group as well as reduction of the nitro group to the corresponding aniline, which underwent partial cyclization with the ester to form tricyclic lactam **33b**. The resultant mixture of cyclized and uncyclized material was treated with DBU to complete cyclization in 41% yield. In a model study, a similar sequence was used to convert **30a** into **33a**, for which we obtained crystals suitable for X-ray crystallography, confirming the expected *cis* ring fusion. Thus, the complete core connectivity of martinellic acid is produced in two linear steps, the shortest preparation of this intermediate to date.

Tricyclic core **33b** was converted to the complete carbon framework of martinellic acid and martinelline in three steps (Scheme 3). Attachment of a Boc group to the amine produced imide **34**. This compound was chemoselectively reduced to the *N,O*-acetal using $LiHBEt_3$ and acetic anhydride.[15] Formation of an *N*-acyliminium ion using $Sc(OTf)_3$ and trapping with allyltrimethylsilane were accompanied by simultaneous loss of the *N*-Boc group in 73% overall yield. A single diastereomer of tricyclic lactam **35** was observed, and the relative configuration was assigned with NOE spectroscopy.[16] Although a related approach using an iminium ion precursor was attempted by Lovely, it was unsuccessful.[14c] We attribute the higher conversion and lack of byproduct formation in our case to the increased reactivity of the *N*-acyl iminium ion intermediate.[17]

(15) (a) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663–1667. (b) Pilli, R. A.; Robello, L. G. *Synlett* **2005**, 2297–2300.

(16) See Supporting Information.

Scheme 3. Completion of the Tricyclic Core of Martinellic Acid and Martinelline



In summary, we report a diastereoselective cycloaddition reaction that is used to produce 1,4,5-trisubstituted γ-lactams. The two-step sequence is synthetically equivalent to the direct reaction of succinic anhydride with imines but more efficient and with higher diastereoselectivity. We have used this process to synthesize the tricyclic core of martinellic acid and martinelline, and we are currently executing a short, enantioselective synthesis of these natural products.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds, as well as X-ray crystallographic data for **24** and **33a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061473Z

(17) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.

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190

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Diastereoselective Synthesis of γ-Lactams by a One-Pot, Four-Component Reaction

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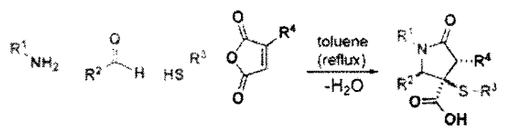
Received August 6, 2007

ABSTRACT



A new one-pot, four-component reaction (4CR) between amines, maleic anhydrides, aldehydes, and thiols has been discovered to form tetra- and pentasubstituted γ-lactams with high diastereoselectivity. Each component is independently variable and employed in equivalent stoichiometry, producing only water as a byproduct.

Multicomponent reactions (MCRs) are an important class of chemical transformations for the efficient synthesis of natural products and screening compounds for the discovery of biological probes and drugs.[1] The Hantsch[2] and Biginelli[3] reactions are important for the synthesis of heterocycles, whereas the Passerini,[4] Ugi,[5] and Petasis[6] MCRs are useful methods for preparing α-hydroxy and α-amino carboxylic acid derivatives.[7] To date, few four-component reactions (4CRs) have been reported to form multiple stereogenic centers with a high level of diastereoselection.[8] Herein, we disclose the first 4CR for the diastereoselective synthesis of γ-lactams wherein either two or three stereocenters are formed with high selectivity.

Our recent discovery of the formal cycloaddition of imines to 2-arylthiosuccinic anhydrides[9] prompted us to probe the mechanism of this reaction. Of particular interest was the high regioselectivity in the attack of the imine on the anhydride. The opening of 2-substituted succinic anhydrides by amine nucleophiles is known to be unselective,[10] presumably due to competing steric and stereoelectronic effects.[11] On the basis of the high regioselectivity required for the yields that we observe, we reasoned that the reactions of anhydride **2** with imines must be reversible (Scheme 1) and that only the isomer with the α-thioaryl substituent (**5a**) was sufficiently enolizable to proceed on to the observed product **6**.

The reversibility of imine attack on anhydride **2** was tested using alternate conditions to access intermediates **3** and **5a**. The reaction of benzylamine with anhydride **2** produces the

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(2) (a) Hantzsch, A. *Liebigs Ann. Chem.* **1882**, *215*, 1–82. (b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980.

(3) (a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962–2967. (b) Kappe, C. O.; Stadler, A. *Org. React. (NY)* **2004**, *63*, 1–116.

(4) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181–189. (b) Banfi, L.; Riva, R. *Org. React. (NY)* **2005**, *65*, 1–140.

(5) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(6) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.

(7) (a) For an example of a five-component reaction in which hexasubstituted benzenes are produced in a one-pot sequential process, see: Janvier, P.; Bienayme, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291–4294. (b) For an example of a seven-component reaction, see: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **1993**, *32*, 563–564.

(8) For direct comparison, we are limiting our description of 3CRs and 4CRs to those in which all of the components can be independently varied. The Hantzsch, Biginelli, Passerini, and Petasis 3CRs and the Ugi 4CR are all examples of MCRs in which each component can, to a certain extent, be varied independently. For a comprehensive discussion of many MCRs discovered to date, see ref 1.

(9) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999–4002.

(10) Stephani, R.; Cesare, V.; Sadarangani, I.; Lengyel, I. *Synthesis* **2002**, 47–52.

(11) (a) Rosenfield, R. E., Jr.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2176–2189. (b) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192–1198.

10.1021/ol701911u CCC: $37.00
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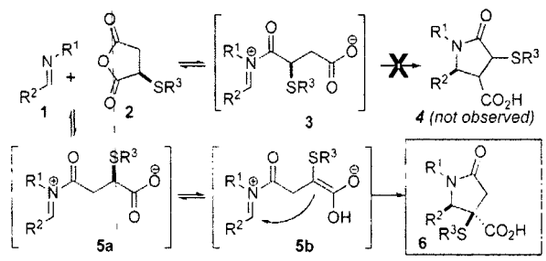
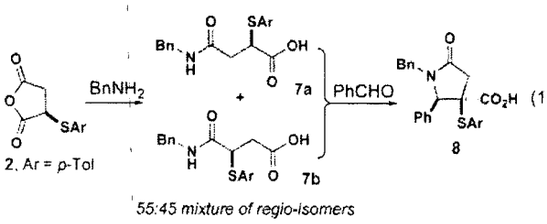
Scheme 1. Reversibility of the Imine–Anhydride Reaction

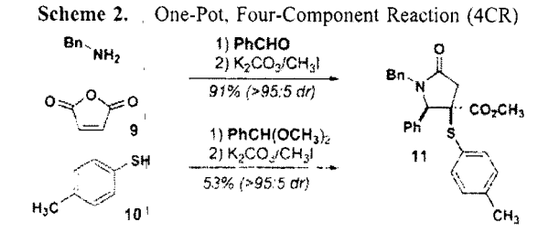


hemi-acid products **7a** and **7b** in a 55:45 ratio (eq 1). The mixture of amides **7a** and **7b** was allowed to react with benzaldehyde in refluxing toluene under dehydrating conditions. Nearly quantitative conversion to lactam **8** was observed. In addition, **7a** and **7b** were prepared, separated, and carried on to **8** in independent reactions.[12] These results are consistent with the intermediacy of *N*-acyl iminium ion **5a** in the formation of lactam **8**. A three-component reaction (3CR) whereby benzylamine, anhydride **2**, and benzaldehyde were combined in a single operation also produced lactam **8** in high yield.



The demonstration that amides **7a** and **7b** produce the same product as the imine anhydride reaction by a completely different mechanism prompted us to attempt a four-component reaction (4CR). We hypothesized that the thiol could react with an initially formed maleic amide to form amides **7a** and **7b** and thus enable a four-component reaction. We were delighted to find that combining benzyl amine, maleic anhydride (**9**), *p*-thiocresol (**10**), and benzaldehyde in toluene at reflux produced lactam **11** in high yield (Scheme 2). Benzaldehyde dimethyl acetal can be used in place of

Scheme 2. One-Pot, Four-Component Reaction (4CR)



benzaldehyde, but the yield is lower. In each case, >95% selectivity for the 4,5-*syn* isomer was observed.

The 4CR of thiols, amines, and aldehydes with maleic anhydride works well for a variety of substrates (eq 2, Figure 1). Alkyl primary amines can be α- or β-branched, as

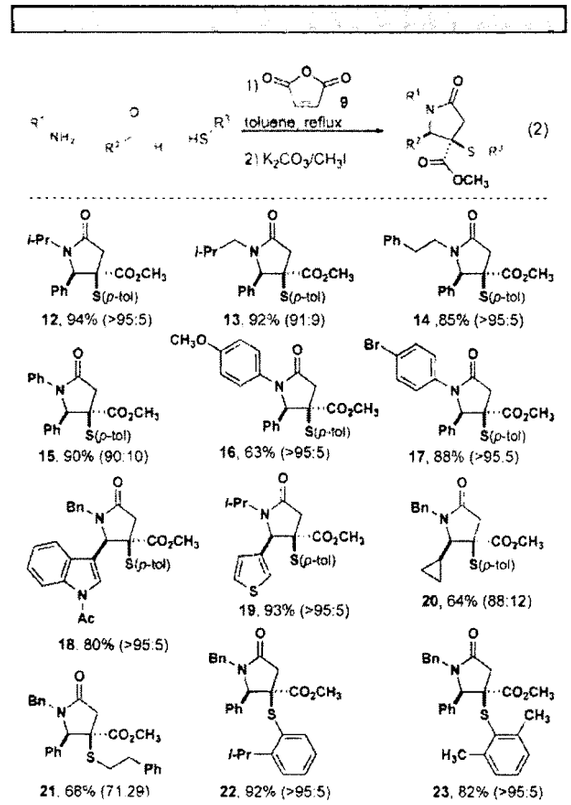


Figure 1. One-pot, four-component syntheses of tetrasubstituted γ-lactams (*p*-tol = *p*-$C_6H_4CH_3$). All reactions were conducted by combining the four components in equimolar ratios and heating to reflux in toluene for 24 h. Yields are reported for conversion to the methyl ester and purification by flash chromatography (see Supporting Information).

previously reported for the imine–anhydride reaction, and in this case, anilines now produce *N*-aryl lactams in excellent yields. Although the reaction is limited to nonenolizable aldehydes due to enamide formation, the successful reaction of cyclopropane carboxaldehyde demonstrates that enolization only needs to be energetically suppressed and not completely prevented. The thiol component can be aryl- or alkyl-substituted, though in the latter case the diastereoselectivity is reduced.[13] Ortho-substitution on the thiols is well tolerated, opening the possibility for asymmetric induction from a substituent with a stereogenic center. Given the importance of γ-lactams in drug discovery and natural

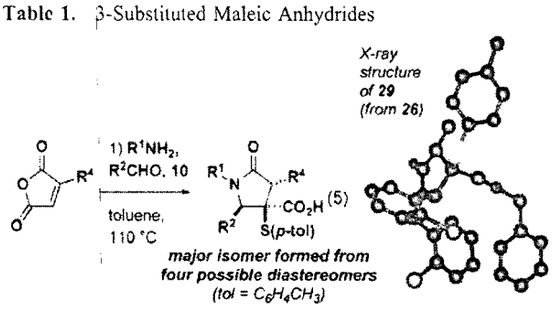
(12) See Supporting Information. A related 3CR with homophthalic anhydride has been observed: Yadav, J. S.; Reddy, B. V. S.; Saritha Raj, K.; Prasad, A. R. *Tetrahedron* **2003**, *59*, 1805–1809.

(13) The *S*-aryl compounds are useful substrates for radical reactions. See: (a) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 1949–1956. (b) Albiex, R.; Bayon, P.; De March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Org. Lett.* **2006**, *8*, 1617–1620. (c) Ghosh, S.; Sinha, S. Drew, M. G. B. *Org. Lett.* **2006**, *8*, 3781–3784.

product synthesis, we anticipate that the wide substrate tolerance will enable the preparation of useful synthetic intermediates.

Pentasubstituted lactams can be prepared from 3-substituted maleic anhydrides (eq 3, Table 1) with high (>83%)

Table 1. 3-Substituted Maleic Anhydrides



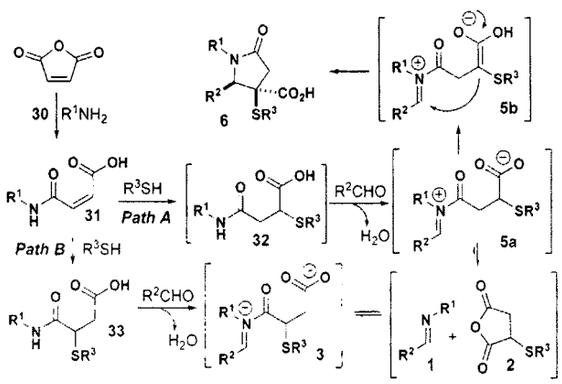
entry (product)	R^1	R^2	R^4	yield[a,b]	ds
1 (**24**)	*i*-Pr	Ph	CH_3	70%	86%[c]
2 (**25**)	Bn	Ph	CH_3	65%	83%[d]
3 (**26**)	*o*-BrC_6H_5	*o*-BrC_6H_5	*i*-Bu	49%[e]	–[f]
4 (**27**)	*i*-Pr	Ph	*i*-Bu	68%	83%[d]
5 (**28**)	Bn	Ph	*i*-Bu	62%	–[f]

[a] Combined yield of product mixture after conversion to the methyl ester (see Supporting Information). [b] Major isomer out of the mixture of up to four isomers. [c] Based on GC analysis of the unpurified mixture of methyl esters. [d] Lower limit based on analysis of ^{1}H NMR spectroscopy. [e] Yield of isolated major diastereomer based on conversion of the intermediate acid to benzyl amide **29** and isolation of the major diastereomer (see Supporting Information). [f] Baseline resolution of a minor isomer was not possible using GC or HPLC.

diastereoselectivity for the formation of one of the four possible diastereomers. Methyl and isobutyl[14] substituents both exhibit high selectivity. The configuration of acid **26** (entry 3) was determined by conversion to benzyl amide **29** and X-ray crystallographic analysis. We are currently investigating the origin of the high diastereoselectivity observed in this reaction.

The mechanism of this new 4CR relies on the ability of both regioisomers of the initially formed maleic amide to converge on a single regioisomer of the iminium ion capable of proceeding to the lactam product (Scheme 3). Reaction of amine **30** with maleic anhydride is rapid at ambient temperature, while the subsequent conjugate addition of the thiol to the amide in the absence of base[15] is slower and proceeds at elevated temperatures. Thiols are known to react

Scheme 3. Mechanism of the One-Pot, 4CR[a]



[a] Iminium ion **3** (path B) equilibrates with iminium ion **5a** (path A) to proceed on to product.

at either terminus (paths A and B, Scheme 3) of the double bond of unsymmetrical maleic amides, depending on the conditions.[16] Condensation with the aldehyde results in the formation of the iminium zwitterions **5a** and **3**, from paths A and B, respectively. In the case of path A, iminium ion **5a** can tautomerize at the thio-substituted carboxylate to form enolate **5b**, which proceeds on to product. In the case of path B, iminium ion intermediate **3** intermediate can partition to imine **1** and anhydride **2**, which can recombine to iminium ion **5a** and proceed on to the observed product. The mechanism for the formation of the pentasubstituted lactam products is complicated by regioselectivity of the reactions of substituted maleic anhydrides,[17] and further control experiments will be required to fully dissect this process.

The products of the 4CR are useful precursors to stereochemically defined trisubstituted lactams. Radical reductive desulfurization yields the corresponding disubstituted carboxy lactam *syn*-**34** in high yield and with high diastereoselection (Scheme 4).[18] The 4,5-*anti* diastereomer of **34** is easily

(14) Alkyl-substituted maleic anhydrides are easily prepared from Grignard reagents and dimethylacetylene dicarboxylate: (a) Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763−770.

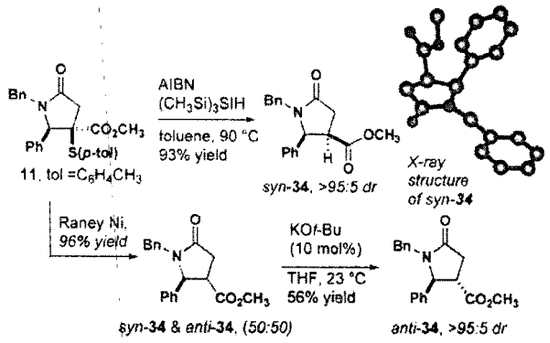
(15) See refs 16a and 16b. The reaction of the thiol with the anhydride in the presence of base is rapid at room temperature: Zienty, F. B.; Vineyard, B. D.; Schleppnik, A. A. *J. Org. Chem.* **1962**, *27*, 3140−3146. When the thiol, amine, and anhydride are combined at rt, some of the thio-substituted anhydride could form since the addition of the amine to the anhydride is probably competitive with the base-mediated conjugate addition of the thiol. Compounds **31**−**33** are all observed in the crude reaction mixture before the reaction mixture is heated to induce the condensation with the aldehyde.

(16) The conjugate addition of thiols to maleic monoamides has been reported to occur at the β-carbon of the amide: (a) Augustin, M.; Mueller, W. *Z. Chem.* **1985**, *25*, 61−62. (b) Neumann, R.; Ringsdorf, H. *J. Am. Chem. Soc.* **1986**, *108*, 487−490. The presence of the other regioisomers is not ruled out in either report. For related studies on thiol conjugate addition to mixed amide/ester and ester/acid maleates, see: (c) Augustin, M.; Koehler, M. *Tetrahedron* **1976**, *32*, 2141−2145. (d) Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1995**, *60*, 6188−6190. (e) Kamimura, A.; Murakami, N.; Kawahara, F.; Yokota, K.; Omata, Y.; Matsuura, K.; Oishi, Y.; Morita, R.; Mitsudera, H.; Suzukawa, H.; Kakehi, A.; Shirai, M.; Okamoto, H. *Tetrahedron* **2003**, *59*, 9537−9546. (f) Kamimura, A.; Murakami, N.; Yokota, K.; Shirai, M.; Okamoto, H. *Tetrahedron Lett.* **2002**, *43*, 7521−7523. (g) Schmidt, T. J.; Ak, M.; Mrowietz, U. *Bioorg. Med. Chem.* **2007**, *15*, 333−342.

(17) (a) Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012−1015. (b) Baydar, A. E.; Boyd, G. V.; Aupers, J.; Lindley, P. F. *J. Chem. Soc., Perkin Trans* **1981**, *1*, 2890−2894. Mehta et al. report that primary amines react unselectively with 3-methylmaleic (citraconic) anhydride, whereas secondary amines were reported to react with >95% regioselectivity. The subsequent report from Baydar demonstrates that these findings were incorrect and that both primary and secondary amines exhibit 50:50 to 78:22 regioselectivity.

(18) (a) Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Ochiai, M. *J. Chem. Soc., Perkin Trans.* **1983**, *1*, 403−411. (b) Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010−3017.

Scheme 4. Stereoselective Synthesis of 4,5-*syn*- and 4,5-*anti*-γ-Lactams



accessed by desulfurization with Raney nickel to a mixture of diastereomers that can be epimerized with potassium *tert*-butoxide at ambient temperature to yield a single isomer of product.

We have demonstrated that densely substituted γ-lactams are formed from a remarkable four-component reaction that forms up to three stereogenic centers in a single step. This reaction should prove useful in the rapid synthesis of collections of compounds for the discovery of drugs and biological probes. We are currently pursuing the synthesis of several natural product targets using this transformation.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds and X-ray crystallographic data for **29** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CCR5 Antagonists as Anti-HIV-1 Agents. 1. Synthesis and Biological Evaluation of 5-Oxopyrrolidine-3-carboxamide Derivatives

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A novel lead compound, *N*-{3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (1), was identified as a CCR5 antagonist by high-throughput screening using [^{125}I]RANTES and CCR5-expressing CHO cells. The IC_{50} value of 1 was 1.9 μM. In an effort to improve the binding affinity of 1, a series of 5-oxopyrrolidine-3-carboxamides was synthesized. Introduction of 3,4-dichloro substituents to the central phenyl ring (10i, IC_{50}=0.057 μM; 11b, IC_{50}=0.050 μM) or replacing the 1-methyl group of the 5-oxopyrrolidine moiety with a 1-benzyl group (12e, IC_{50}=0.038 μM) was found to be effective for improving CCR5 affinity. Compound 10i, 11b, and 12e also inhibited CCR5-using HIV-1 envelope-mediated membrane fusion with IC_{50} values of 0.44, 0.19, and 0.49 μM, respectively.

Key words CCR5 antagonist; chemokine; human immunodeficiency virus type 1 (HIV-1); 5-oxopyrrolidine-3-carboxamide

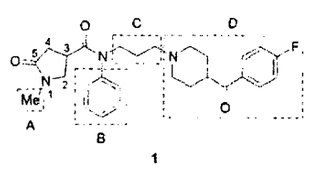
The development of combination antiretroviral therapy with human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors and protease inhibitors has provided a clinically effective method of suppressing viral load in HIV-1-infected individuals, and has resulted in dramatic reductions in HIV-associated morbidity and mortality.[1] However, no current therapies are curative,[2] and HIV-1 replicates again rapidly when treatment ceases.[3] The complexity of the dosing regimens and the toxicity of the current anti-HIV-1 therapy make it difficult to maintain patient compliance.[4] In addition, resistance to the currently available drugs is increasing.[5] Therefore, there remains a need to identify new classes of agents with improved efficacy and less toxicity.

The process of HIV-1 entry into host cells is one of the attractive targets for inhibition of HIV-1 replication.[6] Recent successful studies with enfuvirtide (T-20), a peptide inhibitor of gp41-mediated HIV-1 entry, have confirmed this process as a clinically relevant target.[7] It has been reported that HIV-1 strains that cause the initial infection predominantly utilize CC chemokine receptor 5 (CCR5) as a coreceptor.[8] CCR5-using (R5) HIV-1 is isolated exclusively during the asymptomatic stage, which usually persists for 5 to 10 years.[9] CCR5 is a member of the seven-transmembrane G protein-coupled receptor superfamily.[10] The natural ligands for CCR5 are the CC chemokines [regulated on activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein 1α (MIP-1α), and MIP-1β], which have been reported to inhibit R5 HIV-1 infection *in vitro*.[11] Individuals homozygous for a defect in CCR5 expression have been identified as being highly resistant to HIV-1 infection, while this defect does not cause a significant health problem.[12—14] In addition, infected individuals heterozygous for the defective gene appear to exhibit delayed disease progression.[15] These observations suggest that appropriate, small-molecule CCR5 antagonists functioning as HIV-1 entry inhibitors could be promising anti-HIV-1 therapeutic agents.

Several research groups have reported structurally diverse CCR5 antagonists.[16—22] Our laboratories have previously described the discovery of TAK-779, an anilide derivative with a quaternary ammonium moiety, as a small-molecule CCR5 antagonist.[23,24] Continued screening of Takeda compound libraries using [^{125}I]RANTES and Chinese hamster ovary (CHO) cells expressing human CCR5 has now identified a novel lead compound, *N*-{3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl}-1-methyl-5-oxo-*N*-phenylpyrrolidine-3-carboxamide (**1**), as a CCR5 antagonist (Fig. 1). In this paper, we describe the discovery of the lead compound and the subsequent optimization, focused on a series of 5-oxopyrrolidine-3-carboxamides, to obtain potent CCR5 antagonists which can inhibit the HIV-1 cell entry.

Chemistry

Target compounds were prepared by two general methods as outlined in Charts 2 and 3. The first method (Chart 2) was utilized to investigate structure–activity relationships (SARs) of alkyl linker length (Fig. 1, C) and piperidine moiety modifications (Fig. 1, D). The starting carboxylic acid **2a** was prepared by condensation of itaconic acid and methylamine (Chart 1).[25] Coupling of the carboxylic acid **2a** with aniline using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) gave anilide **3**. Treatment of **3** with sodium hydride followed by the appropriate bromochloroalkane produced chlorides **4a**—**c**. The 2-chloroethyl derivative **4d** was prepared in a different manner as follows. *N*-Alkylation of the anilide **3** with ethyl bromoacetate followed by hydrolysis gave the carboxylic acid. The reduction of the mixed anhydride of the acid gave the alcohol, which on reaction with carbon tetrachloride and triphenylphosphine yielded **4d**. The obtained chlorides **4a**—**d** were coupled with a variety of amines in the presence of



1

Fig. 1. Lead Compound

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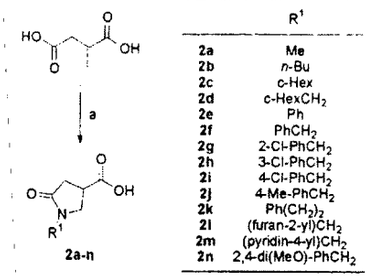
195

potassium iodide and potassium carbonate to provide the target compounds **5a**—**i**. Alternatively, compounds **7a**—**e** were obtained by reductive amination of aldehyde **6** with amines using sodium triacetoxyborohydride. The aldehyde **6** was prepared from the anilide **3** by *N*-alkylation with 2-(2-bromoethyl)-1,3-dioxolane followed by hydrolysis with hydrochloric acid. Benzoylpiperazine derivative **5j** was prepared by hydrogenolysis of benzylpiperazine **5i** followed by benzoylation.

In order to explore the effect of substitutions on the central phenyl ring (Fig. 1, B) and 5-oxopyrrolidine moiety (Fig. 1, A), we investigated an alternate method starting from piperidines **8a, b** (Chart 3). The piperidines **8a, b** were treated with acrolein in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) to afford β-aminoaldehydes *in situ*,[26] which were converted to amine derivatives **9a**—**t** by reductive amination with various aryl or aralkyl amines using sodium triacetoxyborohydride. Coupling reactions of the amines **9a**—**q, s, t** with 5-oxopyrrolidine-3-carboxylic acids **2a**—**n** were carried out *via* the corresponding acid chlorides to afford the targets **10a**—**p**, **11a, b**, **12a**—**m**, **15a, b**. Compound **10q** was prepared by the carbodiimide-mediated coupling of the amine **9r** with the acid **2a**. The carboxylic acids **2b**—**n** were prepared by literature methods[25] from the corresponding amines (Chart 1). Removal of the 2,4-dimethoxybenzyl group of compound **12m** with trifluoroacetic acid (TFA) gave compound **13**, which on *N*-alkylation led to compound **14a, b**.

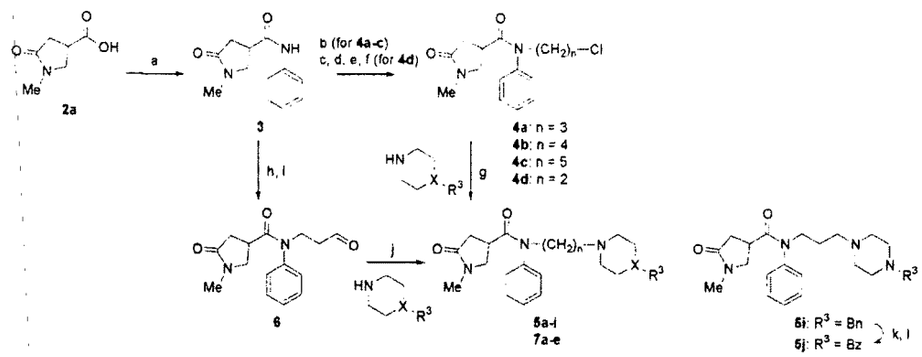
All compounds described were prepared and tested as racemates.



	R^1
2a	Me
2b	*n*-Bu
2c	c-Hex
2d	c-HexCH$_2$
2e	Ph
2f	PhCH$_2$
2g	2-Cl-PhCH$_2$
2h	3-Cl-PhCH$_2$
2i	4-Cl-PhCH$_2$
2j	4-Me-PhCH$_2$
2k	Ph(CH$_2$)$_2$
2l	(furan-2-yl)CH$_2$
2m	(pyridin-4-yl)CH$_2$
2n	2,4-di(MeO)-PhCH$_2$

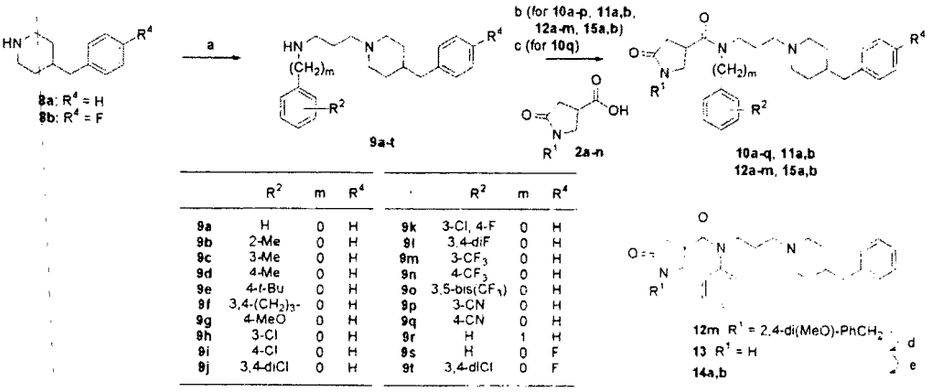
Reagents: (a) R^1NH_2.

Chart 1



Reagents: (a) aniline, EDC, HOBt, DMF; (b) NaH, DMF, then Br-(CH$_2$)$_n$-Cl; (c) NaH, DMF, then BrCH$_2$CO$_2$Et; (d) aq NaOH, MeOH; (e) ClCO$_2$Et, Et$_3$N, THF, then NaBH$_4$, H$_2$O; (f) Ph$_3$P, CCl$_4$; (g) KI, K$_2$CO$_3$, MeCN; (h) NaH, DMF, then 2-(2-bromoethyl)-1,3-dioxolane; (i) aq HCl; (j) NaBH(OAc)$_3$, THF; (k) H$_2$, Pd(OH)$_2$, MeOH; (l) BzCl, Et$_3$N, THF

Chart 2



	R^2	m	R^4		R^2	m	R^4
9a	H	0	H	**9k**	3-Cl, 4-F	0	H
9b	2-Me	0	H	**9l**	3,4-diF	0	H
9c	3-Me	0	H	**9m**	3-CF$_3$	0	H
9d	4-Me	0	H	**9n**	4-CF$_3$	0	H
9e	4-*t*-Bu	0	H	**9o**	3,5-bis(CF$_3$)	0	H
9f	3,4-(CH$_2$)$_3$-	0	H	**9p**	3-CN	0	H
9g	4-MeO	0	H	**9q**	4-CN	0	H
9h	3-Cl	0	H	**9r**	H	1	H
9i	4-Cl	0	H	**9s**	H	0	F
9j	3,4-diCl	0	H	**9t**	3,4-diCl	0	F

Reagents: (a) acrolein, cat. DBU, THF, then R^2-Ph(CH$_2$)$_m$NH$_2$, NaBH(OAc)$_3$; (b) 2, (COCl)$_2$, cat. DMF, DCM, then added to 9, Et$_3$N, DCM; (c) DCC, HOBt, MeCN; (d) TFA; (e) NaH, DMF, then R^1-X

Chart 3