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An Efficient Chiral Moderator Prepared from Inexpensive (+)-3-Carene: Synthesis of the HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor DPC 963

Goss S. Kauffman, Gregory D. Harris, Roberta L. Dorow,[†] Benjamin R. P. Stone, Rodney L. Parsons, Jr., Jaan A. Pesti, Nicholas A. Magnus, Joseph M. Fortunak, Pat N. Confalone, and William A. Nugent*

DuPont Pharmaceuticals Company, Chemical Process R&D, Chambers Works, PRF Building S1, Deepwater, New Jersey 08023

william.a.nugent@dupontpharma.com

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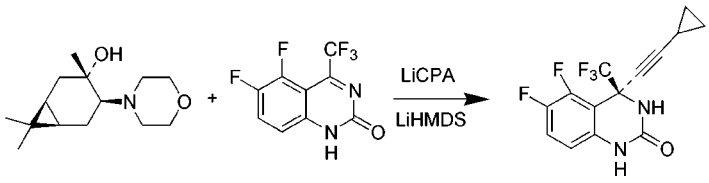
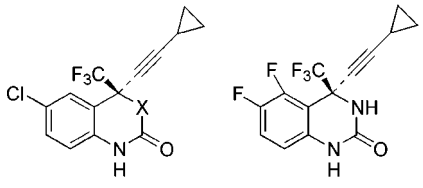
ABSTRACT



The *β*-amino alcohol 4*β*-morpholinocaran-3α-ol is prepared by addition of morpholine to α-3,4-epoxycarane utilizing anhydrous magnesium bromide as Lewis acid promoter. The enantiopure amino alcohol is uniquely effective as a chiral moderator for the addition of lithium cyclopropylacetylide to an unprotected *N*-acylketimine. This reaction provides an efficient route to the second generation NNRTI drug candidate DPC 963.

Sustiva (evavirenz, **1**)[1] is the DuPont Pharmaceuticals Company's HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) which is widely prescribed in the treatment of HIV. The related dihydroquinazolinones DPC 961, **2**, and DPC 963, **3**, are second generation NNRTIs which exhibit increased effectiveness against K103N-containing human immunodeficiency virus as well as other NNRTI-resistant mutant viruses.[2]



1, X = O
2, X = NH

3

A practical and efficient route to DPC 961 has been described[3] and involves the diastereoselective addition of a

[†] Current address: Pharmacia & Upjohn, Kalamazoo, MI.

(1) (a) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Brynes, V. W.; Emini, E. A. *Antimicrobr. Agents Chemother.* **1995**, *39*, 2602−2605. (b) Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Young, S. L.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N. *J. Org. Chem.* **1998**, *63*, 8536−8543. (c) Patel, M.; Ko, S. S.; McHugh, R. J.; Markwalder, J. A.; Srivastava, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S. K.; Trainor, G. L.; Seitz, S. P. *Biooorg. Med. Chem. Lett.* **1999**, *9*, 2805−2810. (d)) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S. K.; Trainor, G. L.; Ko, S. S. *Biooorg. Med. Chem. Lett.* **1999**, *9*, 3221−3224. (e) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937−8940. (f) Tan, L.; Cheng-Yi, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711−713.

(2) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Jeffrey, S.; Bacheler, L. T.; Klabe, R. M.; Diamond, S.; Lai, C.-M.; Rabel, S. R.; Saye, J. A.; Adams, S. P.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *Antimicrobr. Agents Chemother.* **1999**, *43*, 2893−2897.

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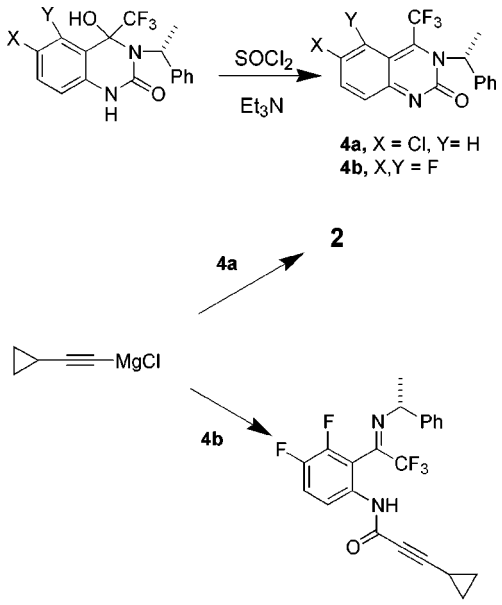
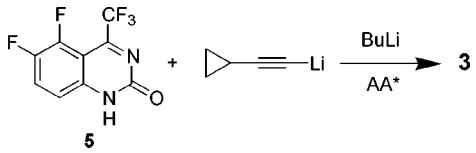
magnesium cyclopropylacetylide to in situ generated azatetraene **4a** as shown in Scheme 1. We were surprised to

Scheme 1

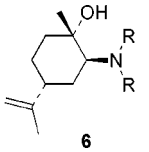


discover that this chemistry fails as a synthetic route to DPC 963. Generation of the corresponding difluoro-substituted azatetraene **4b** and addition of the magnesium acetylide gave exclusively 1,2-addition (Scheme 1).

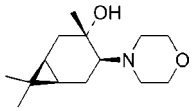
Consequently, we sought an alternative approach to DPC 963 based on the enantioselective addition of lithium cyclopropylacetylide to ketimine **5** as shown below. In the equation, AA* represents a chiral moderator (amino alcohol) which we hoped to recover and recycle. Previous studies[4] on related additions to cyclic *N*-acyl ketimines using norephedrine-derived ligands suggested the possibility of utilizing a chiral β-amino alcohol as a chiral moderator. However, for reasons of efficiency we wished to avoid the N-protection/deprotection protocol required in the earlier studies.



We have previously described[5] a library of β-amino alcohols prepared by straightforward parallel synthesis from enantiopure epoxides and secondary amines. Forty selected β-amino alcohols were rapidly screened as chiral moderators for acetylide addition to **5** following a standard protocol.[6] In general, addition proceeded with low enantioselectivity (<20%) and limited conversion (<30%). A notable exception was a series of limonene oxide-derived amino alcohols **6**[7] which promoted the desired addition in up to 74% enantiomeric excess at 84% conversion. To improve this enantioselectivity, we conceived of **7** as a more rigid, "locked" version of **6**.



6



7

Preparation of **7** proved straightforward[8] as shown below. Epoxidation of inexpensive[9] (+)-3-carene with MCPBA is known[10] to occur exclusively on the face opposite to the cyclopropyl ring to afford the epoxide **8**. Treatment of **8** with morpholine in the presence of magnesium bromide as a Lewis acid promoter[11] afforded **7** contaminated with 4% of an isomeric impurity. The crude product was purified by crystallizing **7** as its 2,4-dihydroxybenzoic acid salt.[12] Pure **7** could then be obtained as a low-melting solid upon free-basing with aqueous sodium hydroxide. The stereochemistry of **7** was confirmed via an X-ray crystal structure.[13] Given the easy synthesis and potential low cost of **7** we find it

(3) Magnus, N. A.; Confalone, P. N.; Storace, L. *Tetrahedron Lett*. **2000**, *41*, 3015−3019.

(4) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem*. **1995**, *60*, 1590−1594. For a review of catalytic asymmetric additions to imines, see: Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069−1094.

(5) Nugent, W. A.; Licini, G.; Bonchio, M.; Bortolini, O.; Finn, M. G.; McCleland, B. W. *Pure Appl. Chem*. **1998**, *70*, 1041−1046.

(6) Screening studies were carried out by adding **5** (0.25 mmol) to a solution of cyclopropylacetylene (1.0 mmol), amino alcohol (0.5 mmol), and butyllithium (1.0 mmol) in THF (5 mL) at 0 °C. After 12 h the reactions were quenched with aqueous KH_2PO_4 and analyzed by chiral HPLC.

(7) Newhall, W. F. *J. Org. Chem*. **1964**, *29*, 185. Amino alcohols **6** used in our initial screen were kindly provided by Prof. Bakthan Singaram and Mr. Will Chrisman of the University of California, Santa Cruz.

(8) In contrast, reaction of (1*S*,3*S*,4*R*)-3,4-epoxycarane with morpholine in the absence of a Lewis acid promoter (100 h, 140 °C) is reported to afford **7** in only 11% yield. Fedyunina, I. V.; Plemenkov, V. V.; Bikbulatova, G. Sh.; Nikitina, L. E.; Litvinov, I. A.; Kataeva, O. N. *Chem. Nat. Compd. (Engl. Transl.)* **1992**, *28*, 173−177.

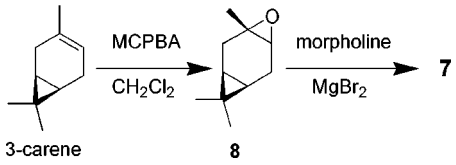
(9) Currently bulk (+)-3-carene (400 lb drums) costs $4.90 per lb.

(10) (a) Brown, H. C.; Suzuki, A. *J. Am. Chem. Soc*. **1967**, *89*, 1933−1040. (b) Sonawane, H. R.; Nanjundiah, B. S.; Shah, V. G.; Kulkarni, D. G.; Ahuja, J. R.; *Tetrahedron Lett*. **1991**, *32*, 1107−1108. (c) Gianini, M.; von Zelewsky, A. *Synthesis* **1996**, 702−706.

(11) To our knowledge this is the first reported use of magnesium bromide to promote the addition of an amine to an epoxide. In contrast, use of $MgBr_2$ to promote *rearrangement* of epoxides is well-known: House, H. O. *J. Am. Chem. Soc*. **1955**, *77*, 5083−5089. Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665−1674. Serramedan, D.; Marc, F.; Pereyre, M.; Filliatre, C.; Chabardes, P.; Delmond, B. *Tetrahedron Lett*. **1992**, *33*, 4457−4460.

(12) **Preparative Details**. Magnesium bromide (12.1 g, 65.7 mmol) is added to a solution of **8** (5.0 g, 32.8 mmol) in morpholine (29.0 mL, 333 mmol). The resulting exotherm warms the mixture to 65 °C. The mixture is heated 16 h at 100 °C. After cooling, water (50 mL) and isopropyl acetate (100 mL) are added, and the mixture is filtered through Celite. The organic phase is separated and the aqueous phase further extracted with isopropyl acetate (50 mL). Distillation of solvent affords crude **7** (6.07 g) as an amber oil. The crude product is dissolved in 95:5 isopropyl acetate/methanol (75 mL), and 2,4-dihydroxybenzoic acid (3.91 g) is added. The mixture is heated to 60 °C and then cooled to 0 °. Filtration and drying affords **7** as its dihydroxybenzoate salt (9.46 g, 73%). Free-basing with excess aqueous sodium hydroxide affords **7** (5.23 g, 66%) as an off-white solid, mp (hexanes) 42−43 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (m, 1 H), 0.72 (m, 1 H), 0.88 (m, 1 H), 0.95 (s, 3 H), 1.01 (s, 3 H), 1.16 (s, 3 H), 1.38 (dd, J = 5.7, 15.9 Hz, 1 H), 1.98 (m, 1 H), 2.07 (dd, J = 9.2, 16.0 Hz, 1 H), 2.44 (dd, J = 3.5, 13.1 Hz, 1 H), 2.52 (m, 2 H), 2.68 (m, 3 H), 3.69 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.69, 17.23, 17.31, 18.66, 24.62, 26.71, 28.82, 35.09, 52.66 (br), 67.94, 72.61, 73.31.

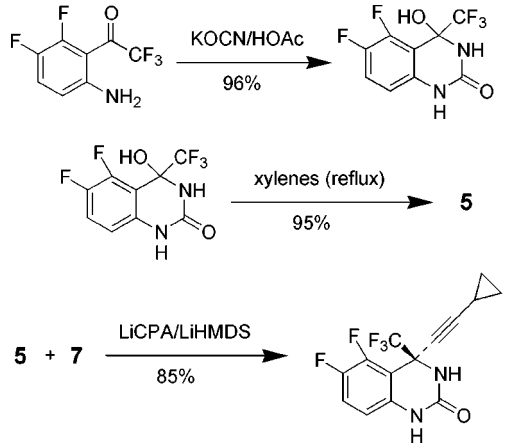
surprising that this known[8] amino alcohol has not been utilized previously as a chiral ligand.



We were pleased to discover that, under our standard conditions, **7** promotes the addition of lithium cyclopropylacetylide to **5** in 80% enantiomeric excess. Optimization of the reaction conditions further improved these results. Lithium bis(trimethylsilyl)amide proved superior to butyllithium or other lithium amides as the strong base in this system. In contrast to previous studies[14] of addition reactions involving lithium cyclopropylacetylide and chiral amino alcohol moderators, a 3:1 ratio of chiral moderator **7** to *N*-acylketimine **5** proved optimal in terms of both yield and enantioselectivity. Under these conditions the *S*/*R* selectivity for LiCPA addition is increased to 97:3.

This chemistry has been applied to the synthesis of DPC 963 as summarized in Scheme 2.[15] Ketimine **5** is prepared

Scheme 2



by treatment of the known[1d] aminoketone with potassium cyanate followed by benzenesulfonic acid-catalyzed dehydration. One molar equivalent of **5** is added to a mixture of **7** (3 equiv), cyclopropylacetylene (3 equiv), and lithium bis(trimethylsilyl)amide (6 equiv) in THF. After 16 h at 0 °C and a further 3 h at 30 °C, extractive workup affords crude **3** in 94% enantiomeric excess. Crystallization from heptane affords DPC 963 in 85% yield and 99.6% enantiomeric excess. Amino alcohol **7** could be recovered unchanged (92% recovery) by basification of the citric acid extracts. The recovered amino alcohol is of suitable purity to be recycled directly.

In summary, we have introduced amino alcohol **7** as an inexpensive ligand for chiral synthesis. Using **7** as a chiral moderator, the potent NNRTI drug candidate DPC 963 has been prepared in three steps and 75% overall yield from a readily available achiral starting material. Additional applications of **7** in asymmetric synthesis are under investigation and will be reported in due course.

Acknowledgment. The authors are deeply grateful to Professor Bakthan Singaram and Mr. William Chrisman for providing the samples of amino alcohols **6** used in our initial scouting studies. We also thank William J. Marshall of DuPont Central Research for determining the crystal structure of compound **7**.

Supporting Information Available: X-ray structure tables for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006321X

(13) Details of the X-ray structure are given as Supporting Information. A noteworthy feature is that four independent molecules of **7** are present in the unit cell. In three of these, the cyclohexane conformation is a twist-boat and the O−C−C−N dihedral angle is in the range 91−96°. In the fourth molecule the conformation is a twist-chair with the OH and morpholine nitrogen in pseudoequatorial positions and the dihedral is 60.2°. Thus, although **7** is clearly more rigid than **6**, the backbone of **7** still possesses significant flexibility.

(14) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028−2038.

(15) **Typical Procedure**. A solution of **7** (4.31 g, 18.0 mmol) and cyclopropylacetylene (1.19 g, 18.0 mmol) in toluene (5.0 mL) was cooled to −5 °C. A 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (36.0 mL, 36.0 mmol) was added, keeping the temperature below 10 °C. The mixture was heated to reflux for 15 min and then cooled to −15 °C. Ketimine **5** (1.50 g, 6.00 mmol) was added, and the mixture was stirred for 16 h at 0 °C and then 3 h at 30 °C. The mixture was cooled to −10 °C and adjusted to pH 7 with 3 N HCl. The organic layer was diluted with heptane (20 mL), the aqueous phase was separated, and amino alcohol **7** was removed by extraction into 1.75 M citric acid (35 mL). The organic layer was washed sequentially with 1 N HCl, 1 N NaOH, saturated NH_4Cl, and water (25 mL each). Volatiles were removed at reduced pressure, and the residue was dissolved in hot heptane (30 mL). On cooling to 0 °C, crystalline (*S*)-**3** was collected by filtration and dried in vacuo (1.62 g, 85% yield, 99.6% ee). Spectroscopic properties were identical to those reported previously (ref 2).