ORGANIC LETTERS

2002
Vol. 4, No. 7
1227−1229

Highly Diastereoselective Nitrone Cycloaddition onto a Chiral Ketene Equivalent: Asymmetric Synthesis of Cispentacin

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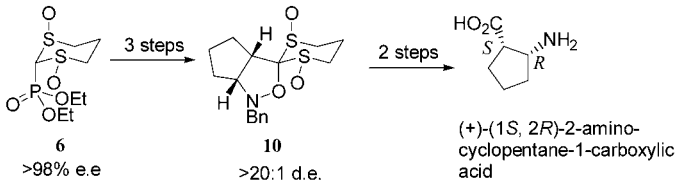
Received February 5, 2002

ABSTRACT



A highly diastereoselective intramolecular nitrone cycloaddition onto a chiral ketene equivalent, obtained by Horner–Wadsworth–Emmons olefination of either enantiomer of bis-sulfinyl phosphonate 6, is described. Cycloaddition gave 5,5-disubstituted isoxazolidine 10 in good yield as a single diastereomer. Catalytic hydrogenolysis of 10 furnished either enantiomer of optically pure *cis*-2-aminocyclopentane-1-carboxylic acid.

Although there are numerous chiral auxiliaries and chiral catalysts for Diels−Alder reactions,[1] there are only a limited number of effective chiral controllers for [3 + 2] cycloaddition reactions.[2] The auxiliaries for these cycloaddition processes are invariably based on chiral acrylate derivatives.[3] We have investigated reagents for the more difficult to access chiral ketene equivalents and have discovered that the ketene dithioacetal **1** is highly effective. This auxiliary shows high reactivity and excellent diastereoselectivity in not only a range of Diels−Alder cycloadditions but also in nitrone cycloadditions as well.[4] As **1** can be easily made in racemic and enantiomerically pure form in four high yielding steps and the bis-sulfinyl moiety can be converted into a carbonyl group, its merits as one of the most effective chiral ketene equivalents available have been demonstrated.

In this paper we report on the further application of sulfoxide-based ketene thioacetals as dipolarophiles in an intramolecular nitrone cycloaddition and its application to a short synthesis of the antifungal antibiotic cispentacin. Cispentacin, (1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid, was isolated from *Bacillus cereus*[5a,b] and *Streptomyces*

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(2) (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(3) Enantioselective cycloaddition reactions of activated nitrones onto ketene acetals have been carried out: (a) Seerden, J. P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843. (b) Seerden, J. P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419.

(4) (a) Aggarwal, V. K.; Drabowicz, J.; Grainger, R. S.; Gültekin, Z.; Lightowler, M.; Spargo, P. L. *J. Org. Chem.* **1995**, *60*, 4962. (b) Aggarwal, V. K.; Gültekin, Z.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771. (c) Aggarwal, V. K.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Org. Chem.* **1998**, *63*, 3481.

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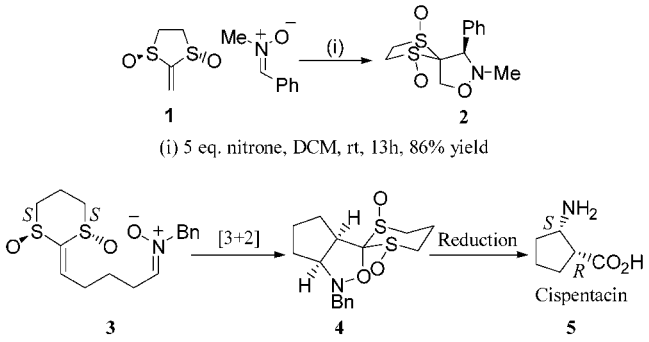
10.1021/ol025665f CCC: $22.00
Published on Web 03/12/2002

setonii[5c,d] and was found to exhibit potent in vivo activity against several *Candida* species in mice.[5] As a result of its biological activity and the inactivity of the unnatural (1*S*,2*R*) enantiomer,[5d] several asymmetric syntheses have been reported.[6]

We have previously studied intermolecular nitrone cycloadditions with **1** and found that the 4,4-disubstituted isoxazolidine **2** was formed exclusively in high yield and with >18:1 diastereoselectivity (Scheme 1). None of the 5,5-disubstituted regioisomer was observed, which was unusual as nitrone cycloadditions with 1,1-disubstituted olefins bearing electron-withdrawing groups normally furnish 5,5-disubstituted isoxazolidines.[7]

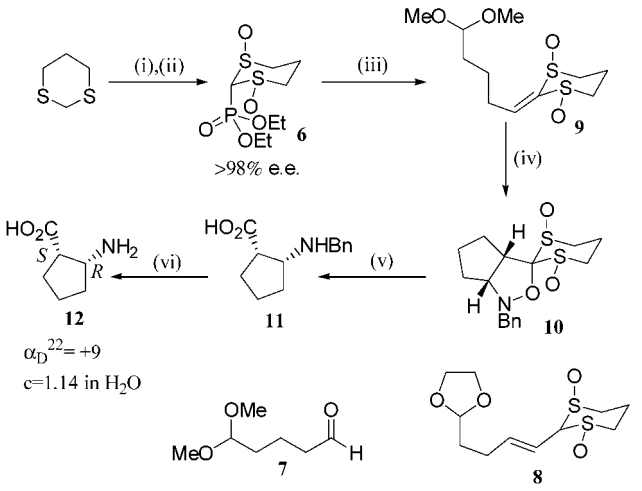
Scheme 1. Diastereoselective Inter- and Intramolecular Nitrone Cycloadditions onto *C2*-Symmetric Ketene Dithioacetals



We reasoned that a 5,5-disubstituted isoxazolidine could be accessed by linking the two components with a suitable tether. A three-carbon tether (**3**)[8] should result in diastereoselective formation of the *cis*-fused 5,5-disubstituted isoxazolidine **4**.[9] Following hydrogenolysis of the N−O and N−Bn bonds, the thioacetal moiety should collapse and directly furnish cispentacin **5** (Scheme 1).

Our synthesis began with dithiane, which was converted into the 2-phosphonate[10] and oxidized to the bis-sulfoxide **6**[8a] using the Modena protocol[11] in good yield and very high enantioselectivity.[12] Attempts to carry out a Horner−Wadsworth−Emmons olefination with glutaraldehyde (as a 25% aqueous solution) under a variety of conditions only led to low yields of the mono- and bis-olefinated products. To avoid the possibility of bis-olefination we decided to employ the terminally differentiated aldehyde **7**, which was readily available by ozonolysis of cyclopentene using the Schreiber procedure.[13] In the event the Horner−Wadsworth−Emmons reaction occurred smoothly with this aldehyde on small scale, but on scale-up, the bond isomerized out of conjugation with the sulfoxides to give **8**.[13c] The problem was solved using a slight deficiency of base (Scheme 2).

Scheme 2. Asymmetric Synthesis of *ent*-Cispentacin[a]



[a] (i) (a) NCS, benzene, rt, 24 h, (b) $P(OEt)_3$, 60 °C, 4 h, 78% yield. (ii) $PhC(CH_3)_2OOH$ (4 equiv), $Ti(O^iPr)_4$ (0.5 equiv), (−)-DET (2 equiv), DCM, 43% yield, >98% ee. (iii) aldehyde (1.5 equiv), $LiOH·H_2O$ (0.99 equiv), THF, 80 °C, 4 h, 80% yield. (iv) $PdCl_2(CH_3CN)_2$ (1 mol %), acetone, 60 °C, 1 h then $BnNH_2OH·Cl$ (1.3 equiv) and $NaHCO_3$ (3 equiv), 60 °C, 4 h, 70% yield. (v) Pd/C (10 mol %), AcOH, H_2 (100 psi), 48 h, 65% yield. (vi) $Pd(OH)_2/C$ (10 mol %), NEt_3 (10 mol %), EtOH, 40 °C, H_2 (1 atm), 4 h, 85% yield.

Attempts to hydrolyze the methoxy acetal **9** under protic conditions were unsuccessful, but use of 1 mol % (bisacetonitrile)palladium(II) chloride in acetone furnished the corresponding aldehyde in excellent yield.[14] The above reaction mixture was used directly in the formation of the nitrone and subsequent [3 + 2] cycloaddition to give **10**. Further-

(6) (a) Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1993**, *41*, 1012. (b) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411. (c) Theil, F.; Ballschuh, S. *Tetrahedron: Asymmetry* **1996**, *7*, 3565.

(7) (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, pp 83−168.

(8) Although dithiolane **1** had been employed in intermolecular nitrone cycloadditions, we chose to work on the dithiane derivative **3** as the synthesis of such substituted alkenes had already been successfully achieved and employed in epoxidation: (a) Aggarwal. V. K.; Barrell, J. K.; Worrall, J. M.; Alexander, R. *J. Org. Chem.* **1998**, *63*, 7128. In related Diels−Alder cycloadditions, dithiolane **1** was found to be more reactive and more selective than the dithiane analogue of **1**: (b) Aggarwal, V. K.; Gültekin, Z.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771. The dithiolane analogue of **3** would have been investigated had low diastereoselectivity been observed in the current nitrone cycloaddition with the dithiane derivative **3**.

(9) (a) LeBel, N. A.; Whang, J. L. *J. Am. Chem. Soc.* **1964**, *20*, 3759. (b) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.*, **1971**, 2440. (c) Baldwin, S. W.; Wilson, J. D.; Aubé, J. *J. Org. Chem.* **1985**, *50*, 4432.

(10) Mlotkowska, B.; Gross, H.; Costisella, B.; Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A. *J. Prakt. Chem.* **1977**, *319*, 17.

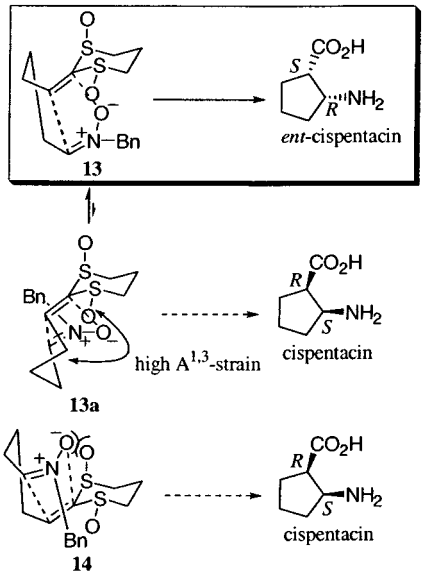
(11) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325−326.

(12) Oxidation of 2-carboethoxy-1,3-dithiane and other 2-substituted 1,3-dithianes with (+)-DET gave the (*R*)-sulfoxide as noted in: (a) Aggarwal, V. K.; Evans, G. R.; Moya, E.; Dowden, J. *J. Org. Chem.* **1992**, *57*, 6390. (b) Aggarwal, V. K.; Esquivel-Zamora, B. N.; Evans, G. R.; Jones, E. *J. Org. Chem.* **1998**, *63*, 7306. (c) Page, P. C. B.; Wilkes, R. D.; Namwinda, E. S.; Witty, M. J. *Tetrahedron* **1996**, *52*, 2125. (d) Samuel, O.; Ronan, B.; Kagan, H. B. *J. Organomet. Chem.* **1989**, *370*, 43.

(13) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 168−171. (c) Initially the 1,3-dioxolane monoacetal was used. For its synthesis, see: Grigorieva, N. Y.; Yudina, O. N.; Moiseenkoz, A. M. *Synthesis* **1989**, *8*, 591.

(14) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

Scheme 3. Competing Transition States in the Cycloaddition

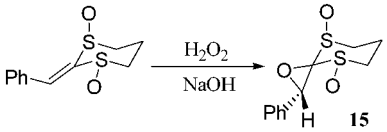


more, this sequence of reactions occurred in high yield (70%) and with complete diastereoselectivity.

We had hoped to be able to reductively cleave the N−O and N−Bn bonds together to furnish cispentacin. However, this was not possible, and so we had to resort to a two-step protocol. Thus hydrogenation of **10** with Pd/C gave the *N*-benzyl amino acid **11**. This was followed by debenzylation using Pearlman's catalyst, but initially this step was not straightforward. Under standard reaction conditions, a mixture of 2-amino-cyclopentane-1-carboxylic acid and its *N*-ethyl derivative was obtained in a 1:1 ratio. The *N*-ethyl derivative presumably originates from palladium-catalyzed oxidation of ethanol to acetaldehyde followed by reductive amination. However, using 5 mol % triethylamine debenzylation was faster, and none of the *N*-ethyl byproduct was observed.[15] Enantiomerically pure *ent*-cispentacin **12** was obtained after a single recrystallization from water/acetone and was spectroscopically identical to literature data.[5d,6c] The absolute stereochemistry of the product was ascertained as being (1*S*,2*R*) from the sign of the optical rotation ($[\alpha]^{22}_D$ +9, c = 1.1 in H_2O) and this provided evidence for the relative stereochemistry of the cycloadduct **10**.

Two factors control the diastereoselectivity of the cycloaddition process: the conformation and face selectivity of the olefin. The preferred conformation of the olefin is **13**, as **13a** suffers from severe $A^{1,3}$ strain.[16] Indeed we have a number of X-ray structures of ketene thioacetal bis-sulfoxides, which all show the same conformation.[17] The face selectivity of the nitrone is opposite to what we had expected on the basis of the diastereoselective epoxidations of related ketene dithioacetals.[8a] In epoxidation the nucleophilic peroxide attacks the top face of the ketene thioacetal to give **15** (Scheme 4), whereas in the intramolecular nitrone cycloaddition the nitrone attacks the lower face, as shown in **13** (Scheme 3). In this case the facial selectivity is controlled by the destabilizing steric and electrostatic interactions between the negatively charged oxygen atom of the (*Z*)-nitrone and the axial sulfinyl oxygen, as depicted in the disfavored TS **14** (Scheme 3).[18,19]

Scheme 4. Diastereoselective Nucleophilic Epoxidation



By using (+)-DET in the Modena oxidation, an asymmetric synthesis of the natural product has been achieved using identical chemistry ($[\alpha]^{22}_D$ −9, c = 1.1 in H_2O).

In conclusion, a highly diastereoselective, intramolecular nitrone cycloaddition onto a chiral ketene equivalent has been used as the key step in an asymmetric synthesis of both enantiomers of *cis*-2-amino-cyclopentane-1-carboxylic acid. $A^{1,3}$ strain and repulsive electronic interactions between the electronegative oxygen atoms of the nitrone moiety and axial sulfinyl group are minimized in the preferred transition state.

Acknowledgment. We thank the EPSRC and Celltech R+D Ltd for CASE Awards to S.J.R. and J.K.B.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For another example of the acceleration of a palladium-catalysed hydrogenolysis using triethylamine as an additive, see: Effenberger, F.; Jager, J. *Chem. Eur. J.* **1997**, *3*, 1370.

(16) For a review on allylic 1,3-strain as a controlling factor in stereoselective transformations, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(17) Barrell, J. K. Ph.D. Thesis, University of Sheffield, 1999.

(18) Acyclic (*E*)-nitrones have been postulated as intermediates in cycloadditions at elevated temperatures: (a) Ishikawa, T.; Saito, S.; Kudo, T.; Shigemori, K. *J. Am Chem. Soc.* **2000**, *122*, 7633. (b) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440. (c) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607. (*Z*)-nitrones formed at lower temperatures have been isolated and characterised using NOE NMR spectroscopy: (d) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686. (e) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1993**, 282.

(19) For a review on the use of the sulfinyl group in asymmetric synthesis, see: (a) Carreno, M. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) Garcia Ruano, J. L. *Top. Curr. Chem.* **1999**, *204 (Organosulfur Chemistry I)*, 1−126.