ORGANIC LETTERS

xxxx
Vol. 0, No. 0
A−D

Cycloaldol Approach to the Isobenzofuran Core of Eunicellin Diterpenes

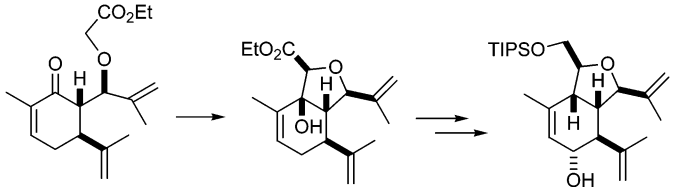
Yonghai Chai, David A. Vicic,[†] and Matthias C. McIntosh*

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701

mcintosh@uark.edu

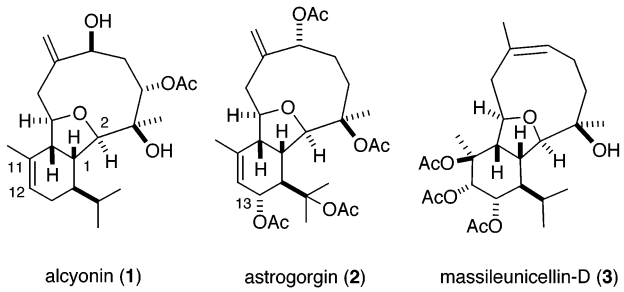
Received January 11, 2003

ABSTRACT



A novel cycloaldol approach to the isobenzofuran core common to many of the eunicellin diterpenes is described. The cycloaldol precursor was prepared by aldol addition of (*S*)-(+)-carvone and methacrolein followed by etherification to a glycolate ester. Chemoselective enolization of the glycolate ester led to the cycloaldol adduct in high yield and diastereoselectivity. An oxidative rearrangement–allylic diazene rearrangement sequence established the requisite cis ring fusion.

The 2,11-cyclized cembranoids are a large family of cembrane-derived natural products of marine origin that include the eunicellins, briarellins, and asbestinins.[1] The eunicellin diterpenes have in common an [8.4.0]tetradecane carbon skeleton. They possess varying levels of oxidation in the cyclohexyl and cyclodecyl rings (Figure 1).[1,2] A common feature of most of the eunicellins is a cis-fused hydroisobenzofuran bicycle.[1]



alcyonin (**1**) astrogorgin (**2**) massileunicellin-D (**3**)

Figure 1. Representative eunicellin diterpenes.

As part of a general approach to the eunicellin diterpenes, we have begun to explore both aldol and Ireland−Claisen rearrangement strategies toward representative members of the eunicellin diterpene family.[3] From a retrosynthetic perspective, we imagined forming the oxononane ring in the latter stages of the synthesis (Scheme 1).[4] We considered the possibility of accessing the isobenzofuran bicycle via a novel cycloaldol reaction of an appropriately substituted

[†] To whom correspondence regarding X-ray crystallographic analyses should be addressed.

(1) Reviews: Wahlberg, I.; Eklund, A.-M. *Prog. Chem. Org. Nat. Prod.* **1992**, *60*, 1−141. Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556.

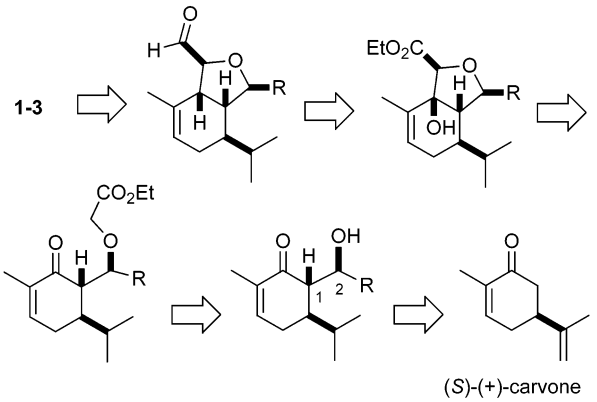
(2) Alcyonin: Kusumi, T.; Uchida, H.; Ishitsuka, M. O.; Yamamoto, H.; Kakisawa, H. *Chem. Lett.* **1988**, 1077−1078. Astrogorgin: Fusetani, N.; Nagata, H.; Hirota, H.; Tsuyuki, T. *Tetrahedron Lett.* **1989**, *30*, 7079−7082. Massileunicellin-D: Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 1561−1575.

(3) Hong, S.-p.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042−2055.

(4) For previous syntheses of eunicellin diterpenes, see: MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674−8680. Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661−8673. Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563−6579. Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135−137. Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021−9032.

10.1021/ol034052f CCC: $25.00
Published on Web 00/00/0000

Scheme 1

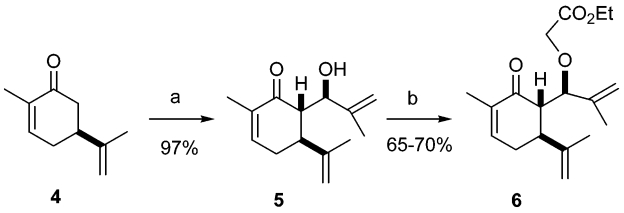


ketoglycolate. The glycolate would in turn be derived from aldol addition of (*S*)-(+)-carvone and the corresponding aldehyde. The intermolecular aldol addition of the (*E*)-enolate derived from carvone would be used install the desired anti stereochemical relationship at C-1 and C-2 common to the eunicellins (cf. Figure 1).

There are scattered reports in the literature of chemoselective enolization of esters or lactones in the presence of nominally more acidic ketones or aldehydes.[5,6] In a few cases, the enolates undergo cycloaldol reactions with the ketone or aldehyde carbonyl group,[5] while in others a different reaction pathway ensues.[6] Burke reported the selective enolization of a glycolate ester in the presence of a cyclopentenone for a subsequent Ireland−Claisen rearrangement.[6a] We felt that a similar chemoselective enolization could be used to induce a cycloaldolization.[7]

The key cycloaldol precursor **6** was prepared from (*S*)-(+)-carvone in two steps (Scheme 2). Intermolecular aldol

Scheme 2[a]

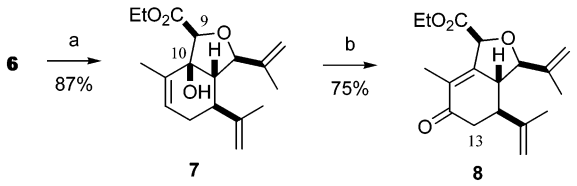


[a] Conditions: (a) LDA, THF, −78 °C, methacrolein, HOAc; (b) Ag_2O, $BrCH_2CO_2Et$, 2,6-lutidine, DMF, 4 °C, 7 days.

addition of (*S*)-(+)-carvone and methacrolein gave *anti*-aldol **5** in excellent yield.[8] Williamson etherification of the sensitive aldol product initially proved to be troublesome. Competitive retro-aldol and β-elimination resulted in only low yields of the desired glycolate being isolated.[9] After considerable experimentation, we found that the combination of Ag_2O and 2,6-lutidine in DMF resulted in formation of glycolate **6** in acceptable yield on a multigram scale. The optimal yield (65−70%) was obtained by performing the reaction for 7 days at 4 °C. The reaction could be performed at considerably shorter reaction times at higher temperatures (24 h, rt), although the yield decreased to ca. 50%.

We were gratified to find that the key cycloaldol reaction occurred smoothly to give isobenzofuran **7** upon treatment of glycolate **6** with KHMDS in THF at −78 °C (Scheme 3).

Scheme 3[a]



[a] Conditions: (a) KHMDS, THF, −78 °C; (b) PCC, silica gel, CH_2Cl_2, rt.

The β-C-9 stereoisomer was the only isomer detected by ^{1}H NMR analysis of the crude reaction mixture. The structural assignment was confirmed by X-ray crystallographic analysis of a derivative (see Supporting Information). The isobenzofuran bicycle was thus accessible in only three steps from (*S*)-(+)-carvone. However, it was necessary to adjust the oxidation level of the cycloaldol product, since the eunicellin diterpenes are not oxygenated at C-10.[1] To this end, an oxidative rearrangement of allylic alcohol **7** was effected to generate enone **8**.[10] The enone could be used to activate the C-13 position as well as introduce the β-hydrogen at C-10 (vide infra).

We sought to install the C-10 hydrogen via an allylic diazene rearrangement (Scheme 4). Such rearrangements have previously been employed to install angular hydrogens in carbocyclic systems via reduction of the corresponding α,β-unsaturated tosylhydrazones.[11] A critical feature of the strategy is the stereochemistry of reduction of the tosylhydrazone, since the rearrangement is a suprafacial process.

(5) Creary, X. *J. Org. Chem.* **1980**, *45*, 2419−2425. Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070−8075. Suzuki, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2821−2825. Pinto, A. C.; Epifanio, R. d. A.; Camargo, W. *Tetrahedron* **1993**, *49*, 5039−5046.

(6) (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221−5228. (b) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288−3300.

(7) For leading references on cycloaldol reactions that do not involve deprotonation, see: Fang, C.; Suganuma, K.; Suemune, H.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1549−1554. Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585−2594. Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551. Molander, G. A.; Brown, G. A.; Storch de Gracia, I. *J. Org. Chem.* **2002**, *67*, 3459−3463.

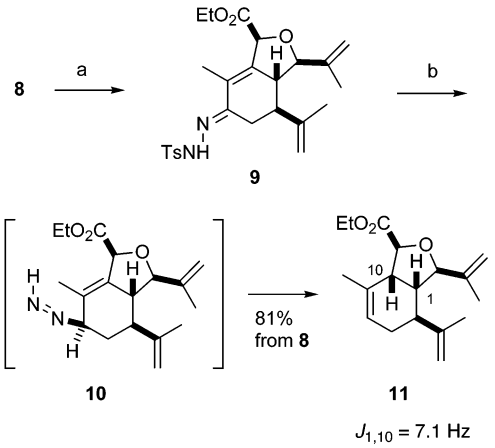
(8) Martin, S. F.; White, J. B. *Tetrahedron Lett.* **1982**, *23*, 23−26.

(9) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Ganett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603−4614. Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett.* **1994**, *35*, 8111−8112.

(10) Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033−1036.

(11) Harapanhalli, R. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3149−3154. Chu, M.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4590−4597. Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009−5012.

Scheme 4[a]



[a] Conditions: (a) $TsNHNH_2$, EtOH, reflux; (b) catecholborane, $NaOAc{\cdot}3H_2O$, $CHCl_3$, from 0 °C to reflux.

Stereoelectronically preferred axial attack of the hydride onto the tosylhydrazone would afford the desired β-stereoisomer of the allylic diazene.[11]

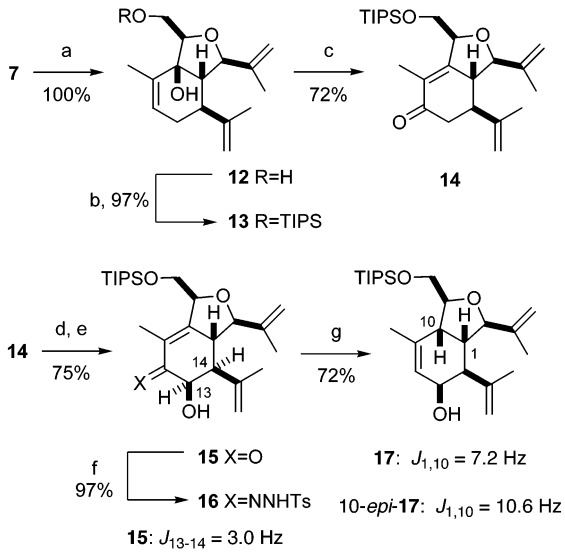
To this end, enone **8** was converted to tosylhydrazone **9** in quantiative yield. Treatment of tosylhydrazone **9** with catecholborane in $CHCl_3$, followed by heating of the reaction mixture under reflux, yielded *cis*-isobenzofuran **11** possessing the alcyonin oxidation level (cf. Figure 1) in 81% yield. The cis ring fusion was assigned on the basis of the $J_{1,10}$ coupling (7.1 Hz).

Our strategy for accessing eunicellins bearing C-13 oxygen substituents was via α-oxidation of the C-12 ketone of enone **8** (cf. Scheme 3). However, the acidity of the C-9 proton led only to oxidation at C-9 or to complex mixtures. Competing enolization at C-9 was circumvented by LAH reduction of the initial cycloaldol **7** to yield diol **12** (Scheme 5). Protection of the primary alcohol as the TIPS ether and oxidative rearrangement as before yielded enone **14**.

Surprisingly, Rubottom oxidation of enone **14** preferentially afforded the undesired β-alcohol **15** as a 7:1 mixture of diastereomers.[12] We elected to defer the epimerization of the C-13 stereocenter until after the allylic diazene rearrangement. Alcohol **15** was treated with tosylhydrazide and HOAc at room temperature in CH_2Cl_2 to afford tosylhydrazone **16**.[13] Reduction with catechol borane as before and allylic diazene rearrangement gave a 4.5:1 ratio of *cis*-hydroisobenzofuran **17** and C-10 *epi*-**17** in 72 and 16% yields, respectively. The stereochemical assignments were consistent with the $J_{1,10}$ couplings.

We were concerned that epimerization of the C-13 β-alcohol would prove to be difficult since the nucleophile

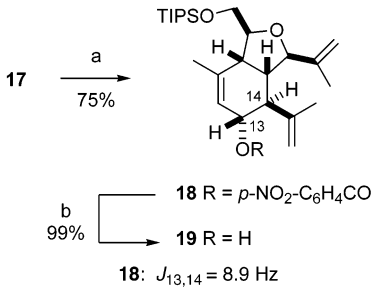
Scheme 5[a]



[a] Conditions: (a) $LiAlH_4$, THF, from −78 °C to room temperature; (b) TIPSOTf, 2,6-lutidine; (c) PCC, Celite, CH_2Cl_2, rt; (d) KHMDS, THF, −78 °C, TMSCl; (e) mCPBA, $NaHCO_3$, hexanes, −20 °C; (f) $TsNHNH_2$, CH_2Cl_2, HOAc, rt; (g) catecholborane, $NaOAc\text{-}3H_2O$, $CHCl_3$, from 0 °C to reflux.

would have to attack the concave face of the cis-fused bicycle. In the event, epimerization of β-alcohol **17** under Mitsunobu conditions occurred smoothly to afford the desired α-*p*-nitrobenzoate ester **18** in 75% yield (Scheme 6).[14] Reductive cleavage of the ester then gave α-alcohol **19**.

Scheme 6[a]



[a] Conditions: (a) DIAD, PPh_3, *p*-nitrobenzoic acid, THF; (b) $LiAlH_4$, ether −78 °C.

In summary, we have found that a novel cycloaldol reaction allows rapid access to the isobenzofuran ring system of the eunicellin diterpenes and related 2,11-cyclized cembranoids. Diastereoselective allylic diazene rearrangements were used to install the requisite cis ring fusion. Applications to the synthesis of several eunicellin diterpenes are currently under investigation.

(12) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−1602.

(13) Under these conditions no epimerization of the C-13 hydroxy group occurred: (a) Garner, C. M.; Mossman, B. C.; Prince, M. E. *Tetrahedron Lett.* **1993**, *34*, 4273−4276. Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974−979. (b) See also: Steinmeyer, A.; Neef, G. *Tetrahedron Lett.* **1992**, *33*, 4879−4882.

(14) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234−236. Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

Acknowledgment. We thank NIH for support of this work (GM-59406 and RR-15569).

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034052F