Novel Asymmetric Route to Carbanucleoside and Prostanoid Intermediates: Efficient Preparation of Both Optical Antipodes of Chiral Cyclopentenone

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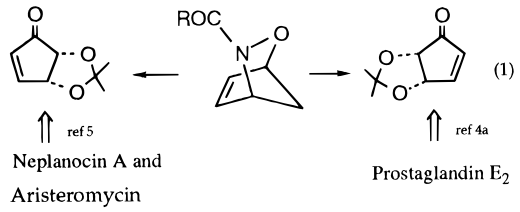
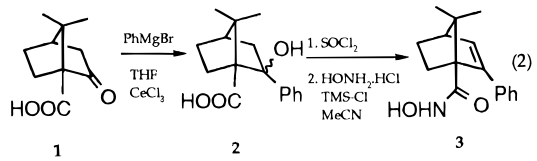
Acylnitroso compounds constitute useful building blocks for synthesis via asymmetric hetero-Diels−Alder reactions because of their potential for further structural elaboration.[1] Extensive research in the chemistry of dihydrooxazine educts derived from cyclohexadienes has led to the development of numerous synthetically important organic transformations;[2] nevertheless, the structural elaboration of the cycloadducts from cyclopentadiene remains far less developed, and its utilization in organic synthesis has therefore been fairly limited.[3] The development of a general approach for the construction of unusual chiral cyclopentenoids would serve to enhance the utility of this cycloaddition reaction. In particular, changing the reaction profile whereby the same dihydrooxazine intermediate could be channeled into both antipodes of cyclopentenone greatly expands synthetic flexibility (eq 1). We wish to record such a chemoselectivity switch in the construction of chiral cyclopentenone, a key intermediate toward several classes of important biologically active compounds ranging from prostaglandin[4] to antiviral carbanucleosides such as neplanocin A and aristeromycin.[5]



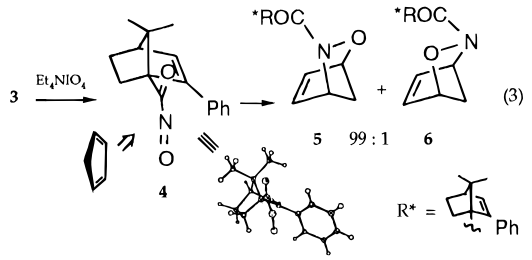
(1)

Earlier work in our laboratories established the feasibility of the camphor skeleton as a chiral source to effect asymmetric additions with excellent stereoselectivity,[6] and we aimed at employing camphor-based acylnitroso to prepare enantiomerically pure dihydrooxazine. The requisite camphor-derived hydroxamic acid was synthesized according to eq 2. Reaction of ketopinic acid **1** with



(2)

2.2 equiv of phenylmagnesium bromide and $CeCl_3$ (2.2 equiv) in THF at −50 °C for 1 h and 25 °C for 3 h afforded the corresponding tertiary alcohol **2** in 92% isolated yield, which upon treatment with $SOCl_2$ at 0 °C for 3 h followed by concentration and immediate treatment with a solution of $HONH_2$·HCl (1.2 equiv) and Me_3SiCl (3 equiv) in CH_3CN initially at 0 °C and then at 25 °C for 6 h provided the desired hydroxamic acid **3** (95% yield). The acylnitroso **4** was generated by *in situ* oxidation of **3** with the salts of periodate (eq 3).[7] Reactions were carried out



(3)

employing the hydroxamic acid **3** as the limiting reagent in the presence of 2.5 equiv of cyclopentadiene. In the preliminary study, we chose to assay cycloaddition diastereoselection as a function of temperature and solvent. As the data in Table 1 show, increasing the reaction temperature from −78 to 0 °C exerts no influence on the reaction stereocontrol (entry 1 vs 3, 2 vs 4).[8a] Switching the solvent from CH_2Cl_2 to MeOH makes virtually no difference in the selectivity and yield of the cycloaddition (entry 1 vs 2, 3 vs 4). Consideration of Dreiding models and molecular modeling[9] suggested that the *s-trans* conformation was the most stable one for acylnitroso **4**,

(1) (a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5, p 419. (b) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088. (c) Kresze G. In *Organic Synthesis in USSR*; Chizhov, O., Ed.; Moscow, 1986; p 169. (d) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (e) Sabuni, M.; Kresze, G. *Tetrahedron Lett.* **1984**, *25*, 5377. (f) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (g) Keck, G. E. *Tetrahedron Lett.* **1978**, *19*, 4767.

(2) (a) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85. (b) Defoin, A.; Poichet, A. B.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 103. (c) Werbitzky, O.; Klier, K.; Felber, H. *Liebigs Ann. Chem.* **1990**, 267. (d) Beier, B.; Schurrle, K.; Werbitzky, O.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2255. (e) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1041. (f) Kirby, G. W.; Nazeer, M. *Tetrahedron Lett.* **1988**, *29*, 6173. (g) Defoin, A.; Schmidlin, C.; Streith, J. *Tetrahedron Lett.* **1984**, *25*, 4515. (h) Felber, H.; Kresze, G.; Braun, H.; Vasella, A. *Tetrahedron Lett.* **1984**, *25*, 5381. (i) Kresze, G.; Kysela, E.; Dittel, W. *Liebigs Ann. Chem.* **1981**, 202. (j) Kresze, G.; Kysela, E. *Liebigs Ann. Chem.* **1981**, 210. (k) Kresze, G.; Dittel, W.; Melzer, H. *Liebigs Ann. Chem.* **1981**, 224. (l) Kresze, G.; Dittel, W. *Liebigs Ann. Chem.* **1981**, 610. (m) Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, *19*, 4763.

(3) (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (b) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1043.

(4) (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *113*, 4726. (b) Babiak, K. A.; Behling, J. R; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *113*, 7441. (c) Kolb, M.; Hijfte, L. V.; Ireland, R. E. *Tetrahedron Lett.* **1988**, *29*, 6769. (d) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *113*, 4726.

(5) (a) Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28*, 4131. (b) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457. (c) Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T. *Tetrahedron Lett.* **1989**, *30*, 1453. (d) Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712.

(6) (a) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (b) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S. *J. Org. Chem.* **1994**, *59*, 8187. (c) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301. (d) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, *61*, 2038.

(7) For *in situ* oxidation of acylnitroso with R_4NIO_4, see refs 1−3.

(8) (a) Proof that **5** had in fact been formed exclusively was gained by conversion to **8**, which upon treatment with D-(+)-camphorsulfonyl chloride and Et_3N at 0−25 °C afforded the corresponding sulfonamide, which showed only a single set of absorptions for the methylene protons (H_2CSO_2−) at δ 3.60 and 3.15 in the 300-MHz NMR spectrum suggestive of complete asymmetric induction. For similar examples of the use of this method, see ref 1e. (b) Belanger, P.; Prasit, P. *Tetrahedron Lett.* **1988**, *29*, 5521.

(9) Energy-optimized acylnitroso structures were determined using Cerius2 (Version 2.0) software (Molecular Simulation, Inc.) with the Dreiding force field: Mayo, S. L.; Olafson, B. D.; Goddard, W. A., III. *J. Phys. Chem.* **1990**, *94*, 8897.

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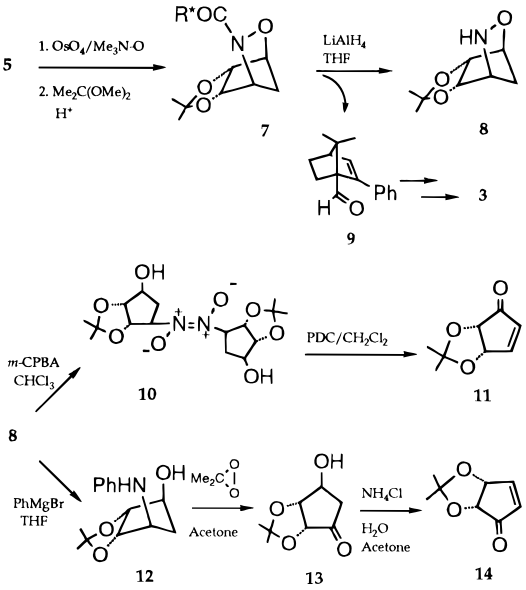
Table 1. Hetero-Diels−Alder Reaction of Acylnitroso 4 with Cyclopentadiene

entry	oxidant	*T* (°C)	solvent	ratio[a] **5**:**6**
1	Et_4IO_4	−78 to −30	CH_2Cl_2	99:1
2	Et_4IO_4	−78 to −30	MeOH	99:1
3	Et_4IO_4	0	CH_2Cl_2	99:1
4	Et_4IO_4	0	MeOH	99:1

[a] Ratios determined by 300 MHz ^{1}H NMR; see ref 8a.

Scheme 1



and the aromatic ring then served as a steric steering group to direct the incoming diene to the *re* face to give adduct **5**. This assignment was confirmed by the successful conversion of **5** into the cyclopentenone **11** and **14** of known absolute configuration (vide infra). Having established that excellent diastereoselectivity was possible with camphor-based chiral auxiliary, we turned our attention to the structural elaboration of **5** (Scheme 1). Dihydroxylation of **5** with catalytic OsO_4 in the presence of trimethylamine *N*-oxide or 4-methylmorpholine *N*-oxide (50 wt % solution in water) at 25 °C for 20 h to give the corresponding diol proceeded from the less hindered α-face. Subsequent conventional acetonide formation afforded the functionalized oxazine **7** in good overall yield (96% for the two steps). Partial reduction of the *N*-acyloxazine **7** with $LiAlH_4$ in THF at 0 °C for 5 h gave the dihydrooxazine **8** (85% yield), $[\alpha]^{23}_D$ +67.4° (*c* = 0.9, $CHCl_3$), along with aldehyde **9**, which could be easily converted to the starting hydroxamic acid **3**. To control the reaction profile in cyclopentenone construction from **3**, cleavage of the N−O bond and then chemoselective oxidation of an amino versus an alcohol were required. We first addressed the oxidative cleavage methodology. Of various oxidizing agents examined, *m*-CPBA proved optimum in precluding ketal ring opening and allowing the N−H bond to be easily oxidized, with concomitant cleavage of the N−O bond. Exposure of **8** to 1.2 equiv of *m*-CPBA in CH_2Cl_2 at 25 °C for 1 h provided dimeric bisnitroso **10**, which upon treatment with pyridinium dichromate in CH_2Cl_2 at 25 °C for 6 h resulted in efficient oxidation of the hydroxyl group and spontaneous elimination of $(NO)_2$ to produce unsaturated ketone **11**, $[\alpha]^{23}_D$ +71.4° (*c* = 3.5, $CHCl_3$) [lit.[4a] $[\alpha]_D$ +71.8° (*c* = 0.91, $CHCl_3$)] in a single step (80% for the two steps). To redirect a reactivity switch for **8** to lead to the antipode of **11**, we devised an alternative route, in which the N−O bond was subjected to reductive cleavage in order to permit the chemoselective oxidation of the amino group. Following trial experiments that served to indicate the need to append a phenyl group to nitrogen, treatment of the electrophilic amination reagent[10] **8** with 3 equiv of phenylmagnesium bromide in THF at −78 to 0 °C for 1 h resulted in reductive cleavage of the N−O bond and *N*-phenyl formation to furnish **12**, mp 107−108 °C, $[\alpha]^{23}_D$ +14.7° (*c* = 1.3, $CHCl_3$), in almost quantitative yield. Exposure of **12** to dimethyldioxirane (as acetone solution[11]) at 0 °C for 3 h smoothly effected the desired chemoselective oxidation to give keto alcohol **13**, mp 84.5−85 °C, $[\alpha]^{23}_D$ −295° (*c* = 1.8, $CHCl_3$) [lit.[8b] mp 83−85 °C, $[\alpha]_D$ −237° (*c* = 1, $CHCl_3$)], in 81% yield. Subsequent dehydration with NH_4Cl in aqueous acetone at 25 °C for 6 h gave enone **14**, $[\alpha]^{23}_D$ −69.9° (*c* = 0.95, $CHCl_3$) [lit.[4a] $[\alpha]_D$ −70.8° (*c* = 0.925, $CHCl_3$)], in 97% yield.

The results reported herein clearly indicate that the chiral bicyclo[2.2.1]oxazine derivative is a valuable building block. Employing the same chiral precursor, this face-selectivity-switch-like method provides an unprecedented entry to both enantiomers of cyclopentenone. This technology represents an attractive synthetic strategy to various structurally related natural products. In addition, this work demonstrates the importance of an appropriately oriented proximal phenyl ring for achieving the exceptionally high levels of asymmetric induction[12] without the aid of a Lewis acid or intramolecular hydrogen bonding.[2e] We believe the above represents a useful working model for designing asymmetric partners in the cycloaddition reaction.

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Supporting Information Available: Full experimental details and analytical data for all compounds (except **10**) (7 pages).

JO970616F

(10) (a) Beak, P.; Kokko, B. J. *J. Org. Chem.* **1982**, *47*, 2822. (b) Kokko, B. J.; Beak, P. *Tetrahedron Lett.* **1983**, *24*, 561. (c) Beak, P.; Basha, A.; Kokko, B. J. *J. Am. Chem. Soc.* **1984**, *106*, 1511. (d) Boche, G.; Wagner, H.-U. *J. Chem. Soc., Chem. Commun.* **1984**, 1591.

(11) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (c) Eaton, P. E.; Wicks, G. E. *J. Org. Chem.* **1988**, *53*, 5353.

(12) For examples of the requirement of a proximal phenyl ring for highly diastereoselective reactions, see: (a) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. (b) Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Smith, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3040. (e) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (f) Whitesell, J. K. *Acc. Chem. Soc.* **1985**, *18*, 280. (g) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.