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MANGANESE(III)-PROMOTED OXIDATIVE FREE-RADICAL CYCLIZATIONS OF β-KETO IMIDES: ASYMMETRIC INDUCTION WITH OPPOLZER'S CHIRAL SULTAM

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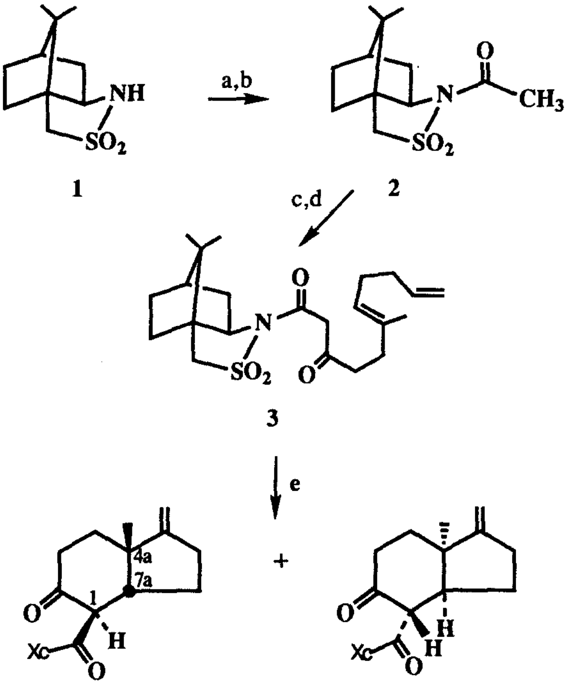
SUMMARY: *Oxidative free-radical cyclization of the unsaturated β-keto imide 3 containing Oppolzer's D-camphor sultam as a chiral auxiliary was studied. Intramolecularly promoted oxidative free-radical cyclization of 3 with Mn (III) in the presence of Cu (II) produced the stereoisomeric cis-hydrindanones 4 and 5 in a 3:1 ratio at 25° C.*

The importance of radical[1] carbon-carbon bond forming reactions in the synthesis of complex organic molecules has become increasingly evident in recent years. However, asymmetric induction in polycyclic intramolecular radical processes still remains a problem. Recently we have shown that oxidative free-radical cyclizations of β-keto esters, containing an appropriately substituted tetraene, with Mn(III) in tandem with Cu(II) afforded stereospecifically a highly functionalized D-homo-5α-androstane-3-one[2] in which seven chiral centers were established in specific relative configurations. We have also demonstrated that these types of oxidative radical cyclizations may serve as an entry to 14-epiestrone[3] and related steroid[4] synthons. Thus, we were interested in the feasibility of designing a system that could provide asymmetric induction in these types of intramolecular radical cyclizations. As a probe toward these ends we choose to study a β-keto imide containing Oppolzer's camphor sultam[5] as the chiral auxiliary. Recently Snider[6] has reported that manganese (III)-based cyclizations of unsaturated β-keto tolyl sulfoxides afforded optically active bicyclo[3.2.1]octan-2-ones but that the corresponding β-keto oxazolidinone did not undergo oxidative cyclization on treatment with Mn(III) and Cu(II) in acetic acid. Herein we wish to report our results on asymmetric inductions utilizing the β-keto imide polyenes 3 and 6.

Reaction of D-camphor sultam 1 with n-BuLi and subsequent acylation with acetic anhydride gave imide 2 (76%; mp 133-34° C), after recrystallization from methanol. Treatment of 2 with two equivalents of lithium isopropylcyclohexylamide (LICA) at -78° C and subsequent acylation with (E)-4-methyl-4,9-nonadienoyl chloride[7] followed by acidification and chromatography afforded keto imide 3[8] (49 %). Oxidative free-radical cyclization of 3, as a 0.1 M solution in deaerated acetic acid, with a 2:1 molar ratio of $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ at 25° C for 4.5 h under Ar gave approximatley a 3:1 ratio of diastereomers 4[9] (49 %; mp 204-206° C, slower moving) and 5 (17 %, mp 221-223° C, faster moving) along with recovered 3 (2 %), after chromatography. The diastereomers were easily separated on silica gel.



Xc = D-camphor sultam

[a]n-BuLi, THF, 0° C, N_2 ; [b]acetic anhydride, 0° C, 1.5 h, 0° C to rt, 4.5 h; [c]2 eq. LICA, -78° C, THF ; [d](E)-4-methyl-4,9-nonadienoyl chloride, THF 30 min, -78° C; then 10% HCl; [e]2 eq. $Mn(OAc)_3 \cdot 2H_2O$, 1 eq $Cu(OAc)_2 \cdot H_2O$, deaerated HOAc, Ar, 4 h, rt.

The C-4a methyl, C-7a methine and the C-1 chiral auxiliary in 4 and 5 were shown to be cis related by transient NOE studies. Irradiation of the angular methyl in each case gave an enhancement of the C-7a methine while no enhancement was observed for the C-1 methine. Crystals of 4 were obtained by slow crystallization from methanol. X-ray-diffraction analysis[10] of 4 proved unequivocally the assigned absolute configuration, Figure 1. The X-ray analysis also shows that the carbonyl group of the imide in 4 is anti disposed to the sulfonyl goup and skewed to the keto group. Both **4** and **5** exist exclusively in the keto form (C-1 methine, $J_{1,7a}$ = 10.7 and 11.1 Hz, respectively) in contrast to the analogous β-keto esters which exist exclusively in the enol form.[3,11] Examination of models suggests that the enol form is destabilized relative to the keto form due to severe steric repulsion between the chiral auxiliary and the hydrindanone system.

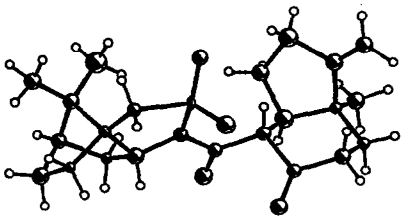
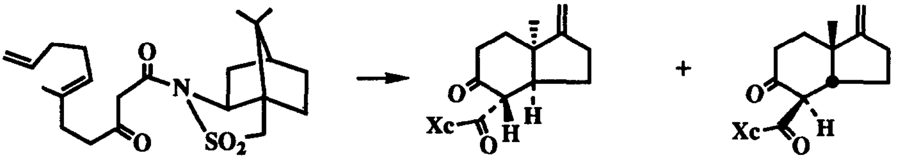


Figure 1 X-ray Structure of **4**

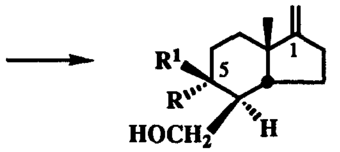
An identical free-radical oxidative cyclization of **6** containing the L-camphor sultam as the chiral auxiliary afforded in the reverse sense diastereomers **7** (slow moving) and **8** (fast moving). The ^1H NMR spectra of **7** and **8** were identical to those of **4** and **5**, respectively.



6 **7** X_c = L-camphor sultam **8**

The chiral auxiliary in **4** was readily cleaved with $NaBH_4$ in isopropyl alcohol (rt, 20 h) to afford in 70 % yield an ~80:20 mixture of diols **9a** (s, δ 0.96) and **9b** (s, δ 1.04) along with a 69 % yield of recovered D-sultam **1**. Reduction of **4** with L-Selectride (Aldrich) in THF followed by oxidative workup with basic hydrogen peroxide yielded almost entirely **9b**. The axial orientation of the secondary alcohol in **9b** is based on the identification of the corresponding C-5 carbinol proton as an equatorial proton from analysis of the COSY spectrum of **9b** and the relative sharpness of this proton (δ 4.18, half band width 8 Hz).

4



9a: R = OH; R^1 = H
9b: R = H; R^1 = OH

Although the degree of selectivity at 25° C is moderate when compared to Lewis acid catalyzed Diels-Alder reactions, aldol condensations and enolate alkylations with comparable sultam chiral auxiliaries[5] at low temperatures, it is still nevertheless impressive as an initial probe of asymmetric induction in polycyclic systems.

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7. Prepared from the corresponding ethyl ester; see reference 3.
8. ^{1}H NMR ($CDCl_3$, δ) data for compounds **2** and **3** are; **2**: 3.86 (m , 1H), 3.48 (AB quartet, 2H, J=14 Hz, 2.41 (s, 3H), 1.16 (s, 3H), 0.98 (s, 3H); **3** (keto-enol mixture): 13.21 (s, enolic OH), 5.72- 5.92 (m, 1H), 5.66 (s, vinylic H of enol), 4.92-5.24 (m, 3H), 3.85 (AB quartet, 2H, J=16.7 Hz), 3.84-3.96 (m, 1H), 3.47 (AB quartet, 2H, J=13.8 Hz), 1.17 (s) and 1.15(s) [3H], 0.97(s) and 0.96(s) [3H].
9. ^{1}H and ^{13}C NMR ($CDCl_3$, δ) for diastereomers **4** and **5** are; **4:** 5.03 (m, 1H), 4.88 (m, 1H), 4.04 (m, 1H), 3.90 (d, 1H, J=10.7 Hz), 3.47 (AB quartet, 2H, J=13.9 Hz), 1.15 (s, 3H), 1.08 (s, 3H), 0.98 (s, 3H); 206.9, 168.9, 156.6, 105.5, 65.6, 58.6, 53.1, 52.1, 48.4, 47.9, 45.1, 44.9, 38.7, 37.2, 33.8, 33.0, 29.3, 28.3, 27.7, 26.3, 21.2, 19.9; **5;** 5.03 (m, 1H), 4.88 (m, 1H), 3.90 (d, 1H, J=11.1 Hz), 3.91 (m, 1H), 3.44 (AB quartet, 2H, J=13.7 Hz), 1.18 (s, 3H), 1.07 (s, 3H), 0.95 (s, 3H); 208.2, 168.7, 156.7, 105.3, 65.3, 58.6, 53.3, 50.0, 48.6, 48.0, 45.0, 44.6, 38.1, 37.5, 33.9, 32.8, 29.3, 28.5, 28.0, 26.6, 20.3, 20.0.
10. Crystal data: $C_{22}H_{31}NO_4S$, M = 405.55, space group $p2_12_12_1$, a = 7.447 (2) Å,b = 11.751 (3) Å, c = 23.716 (7) Å, V = 2075.30 Å^3, Z = 4, d_{calcd} = 1.298 g cm^{-3}. Refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged at R(F) = 0.0939 [Rw(F) = 0.0927] over 2527 reflections with F > 32.33 sigma (F). Additional details may be obtained from Indiana University, Department of Chemistry, Molecular Structure Center, Report # 91228.
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