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Switch in asymmetric induction sense in cycloadditions using camphor-based nitroso dienophiles

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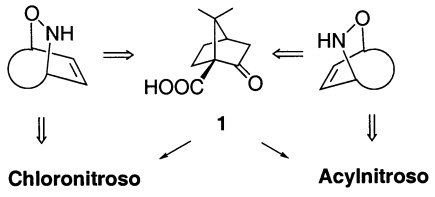
Abstract—We have observed a unique reversal in the absolute stereochemistry of the principal adducts from the cycloadditions of camphor-based acylnitroso dienophiles as compared to the adducts obtained through reactions of the corresponding camphor-based chloronitroso compounds.

1. Introduction

Asymmetric hetero Diels–Alder reactions with *C*-nitroso compounds have gained enormous importance in recent years as they allow ready access to chiral bicyclic dihydrooxazines. Subsequent elaboration of the cycloadducts would deliver unsaturated 1,4-amino alcohols of variable ring size (depending on the diene employed in the reaction) which upon further manipulation would lead to many valuable compounds including carbocyclic nucleosides (five-membered),[1] amaryllidaceae alkaloids (six-membered)[2] and alkaloids such as physoperuvine, epibatidine, calystegine B_2 and tropane (seven-membered).[3] Though there is a plethora of reports on hetero Diels–Alder reactions using chiral nitroso starting materials, including acylnitroso and chloronitroso compounds, these methods suffer from one or more shortcomings such as modest diastereoselectivity, lack of generality, and inaccessibility to both antipodes from the same chiral auxiliary. To date, chloronitroso dienophiles derived from steroids, D-mannofuranose, D-xylofuranose, L-xylose and D-xylose affording high diastereoselectivity have been developed.[3,4] The synthetic flexibility of this methodology would be greatly enhanced if a single readily available chiral auxiliary can be channeled into both enantiomers of a specific molecule simply by changing the reaction profile. Earlier work in our laboratories established the feasibility of employing the same chiral dihydrooxazine as a precursor to prepare both enantiomeric cyclopentenoids.[1c] As a natural extension of the development of chiral nitroso synthons, we were stimulated to evaluate the stereochemical sense of the cycloadditions with acylnitroso and chloronitroso derived from the same chiral ketopinic acid **1** (Scheme 1). We wish to report herein that a unique reversal in the absolute stereochemistry of the principal adducts is observed in the cycloadditions with camphor-based acylnitroso **3** as compared to the adducts obtained through the corresponding reactions of the camphor-based chloronitroso **6** (Scheme 2).

2. Results and discussion

The acylnitroso **3** was generated by in situ oxidation of the chiral hydroxamic acid **2** with periodate salts. The starting hydroxamic acid **2** was readily prepared as follows: one-pot treatment of acid **1** first with $SOCl_2$ at 25°C for 12 h, followed by concentration and immediate treatment with a solution of $HONH_2{\cdot}HCl$ (1.2 equiv.), NEt_3 (5 equiv.) and Me_3SiCl (3 equiv.) in CH_3CN, initially at 0°C and then at 25°C for 8 h afforded **2** in 96% isolated yield. The requisite chloroni-



Scheme 1.

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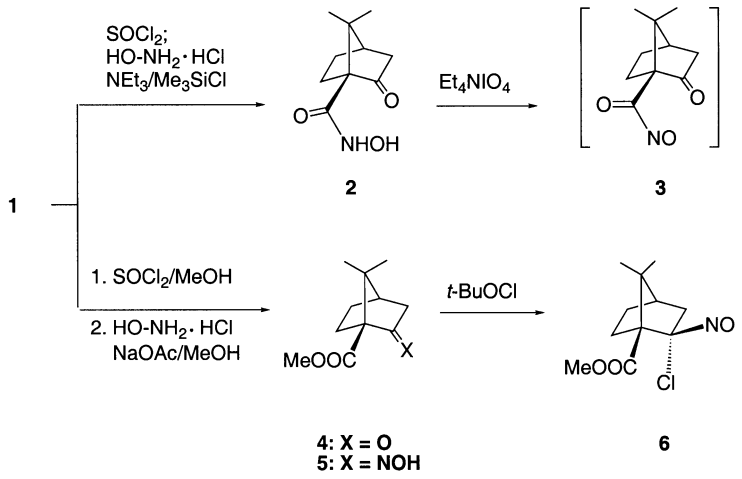
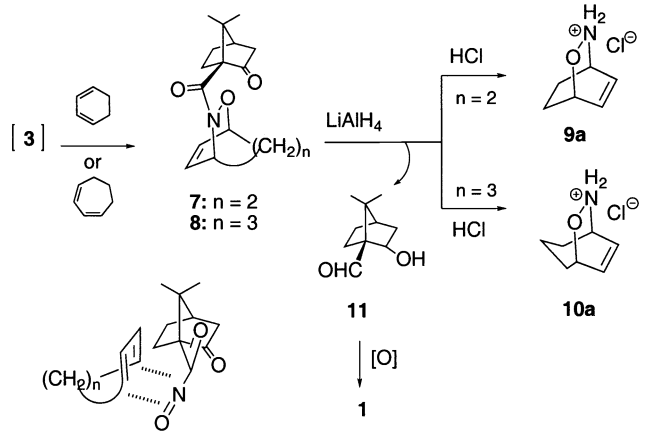


Scheme 2.

troso dienophile **6** was readily prepared from the acid **1** via a three-step protocol: (a) esterification ($SOCl_2$/MeOH, 25°C, 10 h), (b) formation of oxime ($HONH_2$·HCl/MeOH/NaOAc, 65°C, 20 h) and (c) oxidation (t-BuOCl/CH_2Cl_2, 0°C, 6 h). The overall isolated yield of chloronitroso **6** from acid **1** is 88%. The assignment of the position of the nitroso group i.e. *cis* to the CMe_2 bridge was firmly established for **6** by X-ray crystallographic analysis. Exposure of a mixture of **2** and cyclohexadiene (1.5 equiv.) in CH_2Cl_2 to $Et_4N^+IO_4^-$ (1.1 equiv.) at –78°C for 6 h afforded the corresponding cycloadduct in 96% yield as a 91:9 diastereomeric mixture, wherein diastereomerically homogeneous adduct **7** was easily obtained either by recrystallization or by silica gel chromatography in 81% yield (Scheme 3). A closer analysis of the X-ray crystal structure of adduct **7** revealed its absolute stereochemistry. Partial reduction of the *N*-acyloxazine **7** with $LiAlH_4$ in THF at 0°C for 3 h followed by acid treatment led to the corresponding dihydrooxazine hydrochloride **9a** (91% yield), $[\alpha]_D^{25}$ –24.9 (*c* 1.1, MeOH) [lit.[4d] $[\alpha]_D^{25}$ –25.2 (*c* 5.0, $CHCl_3$), lit.[4e] $[\alpha]_D^{25}$ –24.8 (*c* 1.0, MeOH)], along with recovered aldehyde **11**, which could be easily converted to the ketopinic acid. Using cycloheptadiene also gave satisfactory results with acylnitroso **3** where a 94% yield of a 92:8 mixture of



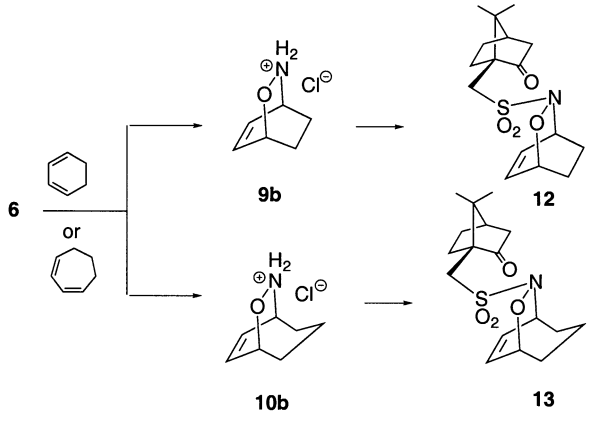
Scheme 3.

diastereomeric adducts was obtained and X-ray crystallographic analysis indicated that the major adduct from the cycloaddition corresponded to the absolute configuration depicted as **8** (78% isolated yield). Reductive cleavage of the *N*-acyl bond of **8** followed by acid treatment gave **10a**, $[\alpha]_D^{25}$ –23.8 (*c* 0.6, H_2O) [lit.[3c] $[\alpha]_D^{25}$ –24 (*c* 1.1, H_2O), lit.[4e] $[\alpha]_D^{25}$ –11.0 (*c* 1.0, EtOH)]. Analysis of both oxazines **9a** and **10a** from the NMR of corresponding D-camphor-10-sulfonamides indicated that they had ee of >98%. Whether the cycloadditions of acylnitroso **3** proceed via the s-*cis* or s-*trans* conformer remains to be established. Semiempirical (AM1) calculations on **3** indicate the s-*trans* conformation of acylnitroso to be 1.24 kcal/mol lower in energy than the s-*cis* conformation. The major adduct from the cycloaddition corresponds to the reaction of the acylnitroso from the s-*trans* conformation assuming an *endo* approach from the less hindered side (Scheme 3). These results are in marked contrast to those of Streith who postulated an s-*cis* acylnitroso conformation to elucidate the sense of asymmetric induction in the cycloadditions of carbamoylnitroso dienophile.[5] In view of the previously reported experimental evidence for the importance of dipole–dipole force in determining the relative energies of transition structures in the aldol reaction,[6] we surmise that a dipole–dipole interactions between ring carbonyl and acylnitroso groups, although difficult to assess, might be an important contributor in influencing the conformer preference. On the other hand, these observations parallel those noted by Procter who has convincingly established through the use of molecular mechanics calculations that a hydrogen bonded to the N=O group in the s-*trans* conformation of acylnitroso derived from mandelic acid might be an important factor governing cycloaddition diastereoselectivity.[7] Interestingly, switching the dienophile from acylnitroso **3** to chloronitroso **6** redirected the sense of asymmetric induction while providing excellent diastereoselectivity and yield. Thus, one-pot treatment of **6** with cyclohexadiene in CH_2Cl_2 at 0°C for 15 h, followed by i-PrOH/H_2O treatment at room temperature to effect hydrolysis of the resulting cycloadduct

provided oxazine hydrochloride **9b** (88%), +24.5 (*c* 1.1, MeOH) [lit.[4d] $[\alpha]_D^{25}$ +22.4 (*c* 5.0, $CHCl_3$)], along with recovered keto ester **5** (92%) (Scheme 4). Sulfonation of **9b** with camphor-10-sulfonyl chloride afforded sulfonamide **12** (mp 131–132°C, $[\alpha]_D^{25}$ +59.2 (*c* 0.6, CH_2Cl_2)). X-Ray crystallographic analysis fully confirms the assigned absolute chemistry. Interestingly, a unique reversal in the absolute stereochemistry of the principal adduct obtained from **6** was observed as compared to the adduct obtained from acylnitroso **3**. More significantly, not only did the 600 MHz ^{1}H NMR spectrum of **12** show only a single set of absorptions for the two diastereotopic protons at C(10) (δ 2.81, d, $J=14.4$ Hz and 3.51, d, $J=14.4$ Hz) , the 150 MHz ^{13}C spectrum showed 16 different absorptions (16 inequivalent C environments). The enantiomeric purity of **9b** was assessed to be >98%. Cycloheptadiene gave an analogous result albeit in somewhat longer reaction time. After stirring at 0°C for 40 h to effect cycloaddition and further treatment with MeOH/1N HCl (25°C, 2 days) to effect hydrolysis, the desired oxazine hydrochloride **10b**, $[\alpha]_D^{25}$ +24.2 (*c* 0.8, H_2O) [lit.[3c] $[\alpha]_D^{25}$ +24 (*c* 1.0, H_2O)], was isolated in 71% yield. Assignment of the absolute configuration of the bicyclic oxazine was provided, as before, by conversion of **10b** to sulfonamide **13**, (mp 108–109°C, $[\alpha]_D^{25}$ +88.9 (*c* 1.4, CH_2Cl_2)), and examination of its X-ray crystal structure. Again, the sense of asymmetric induction is opposite to that obtained from acylnitroso **3** and was in accord with our expectation that the diene approaches preferentially from the less hindered face of the nitroso i.e. *syn* to the chlorine atom. In addition, it was not surprising to observe that the sulfonamide **13** showed only a single set of the two doublet absorptions for the C(10) methylene protons in the 600 MHz ^{1}H NMR spectrum, suggestive of complete asymmetric induction (δ 2.91 and 3.57, $J=15$ Hz).

3. Conclusion

We have demonstrated a novel example to illustrate a stereocontrolled chiral oxazine synthesis. These results represent, to our knowledge, the first example of employing the same chiral auxiliary to obtain different chiral nitroso synthons for construction of both antipodes of bicyclic oxazines in high enantioselectivity through cycloaddition. The fact that chloronitroso **6** provides exceptionally high levels of asymmetric induction enhances its importance as a chiral nitroso synthon. Significantly, the remarkable ease of preparation of **2** and **6**, together with non-destructive chiral auxiliary removal make camphor-based nitroso compounds attractive choices for asymmetric cycloadditions.



Scheme 4.

4. Experimental

4.1. General procedure

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR 300 (300 75 MHz) or 400 (400 100 MHz). IR spectra were recorded on a Perkin–Elmer FT-IR 1750. Optical rotations were measured with a Perkin–Elmer P 241 polarimeter in a 10 cm cell with the solvent indicated.

4.2. (+)-Ketopinohydroxamic acid 2

A magnetically stirred solution of ketopinic acid **1** (3.67 g, 20 mmol) and $SOCl_2$ (35 mL) was stirred at room temperature for 12 h, concentrated, and treated with a solution of $HONH_2{\cdot}HCl$ (1.68 g, 24 mmol), NEt_3 (13.9 mL, 100 mmol) and Me_3SiCl (7.7 mL, 60 mmol) in CH_3CN (100 mL) at 0°C. After 8 h at 25°C, the solvent was evaporated, and the residue was taken up in CH_2Cl_2, washed with water, dried, concentrated and chromatographed on silica gel (elution with 33% EtOAc/hexane) to afford **2** as a white solid (3.8 g, 96%): mp 106–107°C; IR (neat) 3276, 1732, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (bs, 1H), 7.89 (bs, 1H), 2.62–2.48 (m, 2H), 2.22–2.01 (m, 3H), 1.68–1.43 (m, 2H), 1.26 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.97, 166.80, 64.08, 50.45, 45.76, 43.42, 27.97, 27.55, 20.60, 20.24; $[\alpha]_D^{25}$ +91.0 (*c* 0.5, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{10}H_{15}NO_3$: 197.1055, found: 197.1058.

4.3. Methyl (1*R*,2*S*)-2-chloro-2-nitroso-1-bornanecarboxylate 6

A magnetically stirred solution of ketopinic acid **1** (9.15 g, 50 mmol) and $SOCl_2$ (75 mL) was stirred at room temperature for 12 h, concentrated, and treated with MeOH (250 mL). After 10 h at 25°C, NaOAc (16.4 g, 200 mmol) and $HONH_2{\cdot}HCl$ (4.2 g, 60 mmol) were added, and the mixture was heated at 70°C for 45 h. The solution was concentrated, and the residue was taken up in CH_2Cl_2, washed with water, dried and concentrated. The crude oxime **5** taken up in CH_2Cl_2, cooled to 0°C, and treated dropwise with *t*-BuOCl (5.6 g, 52 mmol). After 10 h, the reaction mixture was concentrated and chromatographed on silica gel (elution with hexane) to afford **6** as a blue solid (10.8 g, 88%): mp 27–28°C; IR (neat) 2958, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 2,85 (dt, $J=14.8$, 3.6 Hz, 1H), 2.59–2.52 (m, 1H), 2.36–2.29 (m, 1H), 2.09–2.06 (m, 1H), 2.05–2.01 (m, 1H), 1.62 (d,

$J=14.8$ Hz, 1H), 1.57–1.49 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.91, 119.65, 65.88, 52.79, 51.65, 46.20, 41.97, 31.24, 26.82, 22.87, 22.11; high-resolution MS (FAB+) m/e calcd for $C_{11}H_{16}ClNO_3$: 246.0819, found: 246.0811.

4.4. (1*R*,2*S*)-2-[(1′*S*,2′*R*)-2-oxo-1-Bornylcarbonyl]-2-aza-3-oxabicyclo[2.2.2]-5-octene 7

To a solution of **2** (395 mg, 2.0 mmol) and 1,3-cyclohexadiene (0.23 mL, 2.4 mmol) in CH_2Cl_2 (5 mL) at −78°C was added $Et_4N^+IO_4-$ (0.7 g, 2.2 mmol). After 6 h the reaction mixture was concentrated and chromatographed on silica gel (elution with 30% EtOAc/hexane). There was isolated 0.45 g (81%) of **7** as a white solid: mp 108–109°C; IR (neat) 1736, 1639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (dd, $J=$ 6.0, 3.0 Hz, 1H), 6.47 (dd, $J=6.0$, 3.0 Hz, 1H), 5.23–5.16 (m, 1H), 4.63–4.57 (m, 1H), 2.41–2.31 (m, 2H), 2.18–2.08 (m, 3H), 1.97–1.78 (m, 3H), 1.41–1.22 (m, 3H), 1.14 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.97, 166.80, 134.22, 133.45, 78.44, 64.08, 50.45, 45.76, 43.45, 43.42, 27.97, 27.92, 27.55, 20.60. 20.24, 8.57; $[\alpha]_D^{25}$ +37.6 (c 2.0, CH_2Cl_2); high-resolution MS m/e calcd for $C_{16}H_{21}NO_3$: 275.1514, found: 275.1513. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.09. Found: C, 69.39; H, 7.64; N, 5.21%.

4.5. (1*R*,2*S*)-2-[(1′*S*,2′*R*)-2-oxo-1-Bornylcarbonyl]-2-aza-3-oxabicyclo[3.2.2]-8-nonene 8

To a solution of **2** (395 mg, 2.0 mmol) and 1,3-cycloheptadiene (0.26 mL, 2.4 mmol) in CH_2Cl_2 (5 mL) at −78°C was added $Et_4N^+IO_4-$ (0.7 g, 2.2 mmol). After 6 h, the reaction mixture was concentrated and chromatographed on silica gel (elution with 16% EtOAc/hexane) to give 0.46 g (78%) of **8** as a white solid: mp 135–136°C; IR (neat) 1741, 1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, $J=6.3$, 3.0 Hz, 1H), 6.20 (dd, $J=6.3$, 3.0 Hz, 1H), 5.22–5.16 (m, 1H), 4.60–4.56 (m, 1H), 2.48–2.39 (m, 1H), 2.36–2.11 (m, 3H), 1.98–1.27 (m, 9 H), 1.19 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.20, 164.70, 129.88, 127.19, 76.53, 66.98, 51.08, 49.66, 43.91, 43.73, 28.67, 26.83, 26.63, 21.75, 21.68, 20.54, 18.73; $[\alpha]_D^{25}$ +40.6 (c 2.0, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{23}NO_3$: 289.1672, found: 289.1670.

4.6. (1*S*,4*R*)-3-Aza-2-oxabicyclo[2.2.2]-5-octene-hydrochloride 9a and intermediate 11

To a solution of **7** (550 mg, 2.0 mmol) in THF (5 mL) at 0°C was added $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol). After 2 h at room temperature, the reaction mixture was cooled to 0°C, treated dropwise with water and extracted with ether (2×20 mL). The combined organic extracts were extracted with HCl (0.5N, 2×4 mL). The ether layer was concentrated to give the epimeric hydroxy aldehydes **11**, as evidenced by the aldehydic ^{1}H NMR signals at δ 9.84 and 9.75. The unstable intermediate **11** was immediately taken up in acetone (5 mL), cooled to 0°C and treated dropwise with Jones' reagent until a reddish-yellow color persisted. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried and concentrated to give the recovered ketopinic acid **1** (310 mg). Evaporation of the combined aqueous layers afforded **9a** as a white solid (0.27 g, 91%): mp 135–136°C; ^{1}H NMR (400 MHz, D_2O) δ 6.69 (dd, $J=7.6$, 6.8 Hz, 1H), 6.42 (dd, $J=7.6$, 6.8 Hz, 1H), 4.81–4.79 (m, 1H), 4.43–4.39 (m, 1H), 2.07–1.92 (m, 2H), 1.45–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.28, 128.08, 71.49, 49.04, 21.39, 16.70; $[\alpha]_D^{25}$ −24.5 (c 1.1, MeOH); high-resolution MS m/e calcd for C_6H_9NO: 111.0684, found: 111.0686.

4.7. (1*R*,5*S*)-7-Aza-6-oxabicyclo[3.2.2]-8-nonene-hydrochloride 10a and intermediate 11

To a solution of **8** (578 mg, 2.0 mmol) in THF (5 mL) at 0°C was added $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol). After 2 h at room temperature, the reaction mixture was cooled to 0°C, treated dropwise with water and extracted with ether (2×20 mL). The combined organic extracts were extracted with HCl (0.5N, 4 mL×2). The ether layer was concentrated to give the epimeric hydroxy aldehydes **11** as evidenced by the aldehydic ^{1}H NMR signals at δ 9.84 and 9.75. As described above the ether layer was concentrated and the residue was immediately oxidized to give the recovered ketopinic acid **1** (305 mg). Evaporation of the combined aqueous layers afforded **10a** as a white solid (0.29 g, 90%): mp 150–151°C; IR (neat) 1741, 1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, $J=5.6$, 4.0 Hz, 1H), 6.39 (dd, $J=5.6$, 4.0 Hz, 1H), 4.89–4.86 (m, 1H), 4.58–4.55 (m, 1H), 2.37–2.31 (m, 1H), 2.07–1.97 (m, 2H), 1.91–1.85 (m, 1H), 1.65–1.60 (m, 1H), 1.41–1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.77, 125.10, 77.43, 54.12, 30.61, 26.11, 17.79; $[\alpha]_D^{25}$ −22.5 (c 0.8, H_2O); high-resolution MS m/e calcd for $C_7H_{12}NO$: 126.0910, found: 126.0909.

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