Asymmetric cycloadditions of dienes to chloronitroso compounds derived from carbohydrate ketones: syntheses of (−)-physoperuvine and (+)-epibatidine

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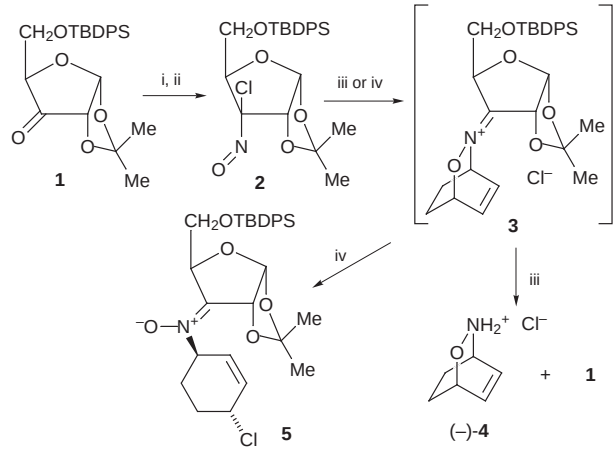
An α-chloronitroso compound derived from D-xylose undergoes cycloadditions with cyclic dienes to give bicyclic dihydrooxazines of high enantiomeric purity; such adducts were used in a synthesis of (−)-physoperuvine and a formal synthesis of (+)-epibatidine, whilst a pseudoenantiomeric chloronitroso compound is also available from L-sorbose.

There has been considerable interest in recent years in the development of asymmetric versions of the hetero-Diels–Alder cycloaddition[1] of dienes with *C*-nitrosocompounds to form 3,6-dihydro-1,2-oxazines, since the further manipulation of the initial cycloadducts can be used to prepare a wide range of nitrogen-containing organic compounds. Most work has been done using acylnitroso compounds bearing a chiral auxiliary,[2] although the removal of the auxiliary can involve conditions that are not compatible with sensitive functionality. Studies have also been carried out using chiral α-chloronitroso compounds, since in the presence of a nucleophilic solvent solvolysis of the initial cycloadduct occurs to liberate the dihydrooxazine directly. After initial work with steroidal chloronitroso compounds,[3] there has been emphasis on the use of chloronitroso compounds derived from carbohydrate hydroximino lactones.[4,5] We were attracted to the use of chloronitroso compounds derived from readily-available and sterically-rigid carbohydrate ketones; we now report that such systems can give very high degrees of enantioselectivity, whilst also regenerating the auxiliary in high yield and in a form in which it can be easily recycled. We also describe the use of one of our auxiliaries[6] in asymmetric syntheses of two natural products.

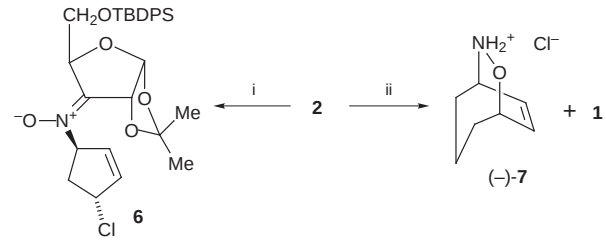
Thus, 1,2-*O*-isopropylidene-α-D-xylofuranose,[7] was selectively silylated and then oxidized (PCC, molecular sieves) to give ketone **1** (Scheme 1). Conversion of **1** to its oxime (mixed isomers) and subsequent treatment with *tert*-butyl hypochlorite gave the α-chloronitroso compound **2** (69% overall from D-xylose) as a blue crystalline solid. That chlorination had occurred from the *exo*-face was confirmed by X-ray crystallography, which also indicated the eclipsed nature of the chloronitroso unit[8] (dihedral angle Cl–C–N–O, 0.8°).



Scheme 1 *Reagents and conditions*: i, $NH_2OH·HCl$, $NaHCO_3$, EtOH–H_2O; ii, Bu^tOCl, CH_2Cl_2; iii, cyclohexa-1,3-diene, $CHCl_3$–Pr^iOH–H_2O (100:100:1), 0 °C; iv, cyclohexa-1,3-diene, $CHCl_3$, 0 °C

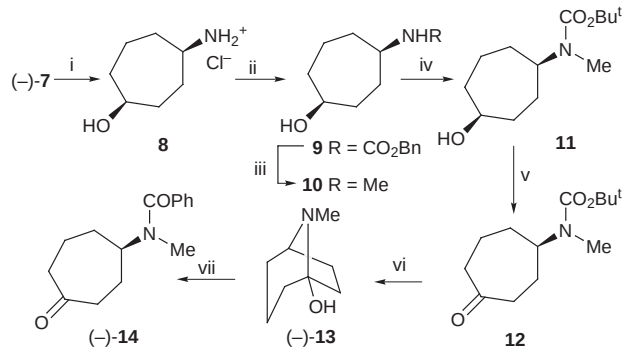
Treatment of **2** with cyclohexa-1,3-diene in $CHCl_3$–Pr^iOH containing water (1%) gave the cycloadduct (−)-**4** (94%), together with ketone **1** (95%), which could be recycled. The absolute configuration of (−)-**4** followed from the sign of its optical rotation,[4a,5] and the enantiomeric excess (ee) was shown to be 96% by reaction of (−)-**4** with (+)-camphor-10-sulfonyl chloride and integration of the two pairs of doublets for the diastereotopic protons at C-10 [major isomer from (−)-**4**, δ 2.91 and 3.37; minor isomer from (+)-**4**, δ 2.76 and 3.47].[4a] In contrast, when the reaction of **2** with cyclohexadiene was carried out in a non-nucleophilic and non-coordinating solvent ($CHCl_3$), only the nitrone **5** (69%) was obtained, a result that can be rationalized as occurring by attack of chloride ion on the intermediate iminium ion **3**.‡

Reaction of **2** with cyclopentadiene (Scheme 2) did not give any bicyclic dihydrooxazine under any conditions investigated. Instead, the only product isolated, even in the presence of nucleophilic solvents, was the nitrone **6** (93% in $CHCl_3$), and attempts to divert the course of reaction by addition of silver salts were unsuccessful. The structure of **6**, including the stereochemistry of the C=N double bond, was confirmed by X-ray crystallography. On the other hand, reaction of **2** with cyclohepta-1,3-diene in the presence of water gave only the bicyclic adduct (−)-**7** {$[\alpha]_D$ −11.0 (*c* 1.0, EtOH)} (93%) and ketone **1** (93%). Derivatization of **7** with camphor-10-sulfonyl chloride and analysis by ^1H NMR spectroscopy led to an estimated ee of ⩾96%. The pattern of reactivity shown by **2** as the diene is varied presumably reflects the degree of ring strain present in the intermediate iminium ions (**3** and the equivalent structures). The stereochemistries of (−)-**4** and (−)-**7**, and of **6**, can be rationalized in terms of cycloadditions occurring through *exo*-transition states on the less hindered *si*-face of the nitroso group, away from the isopropylidene unit.



Scheme 2 *Reagents and conditions*: i, cyclopentadiene, $CHCl_3$, room temp; ii, cyclohepta-1,3-diene, $CHCl_3$–Pr^iOH–H_2O (100:100:1), 4 °C

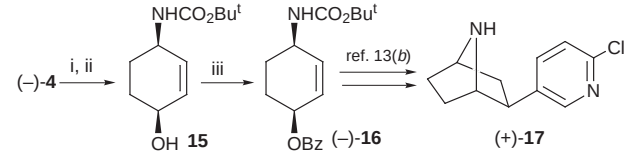
The cycloadduct (−)-**7** was used in an enantioselective synthesis of (−)-(*R*)-physoperuvine [(−)-**13**] (Scheme 3), the *S*-enantiomer of which is the major alkaloid of *Physalis peruviana* Linne.[9] Physoperuvine has been synthesized as a racemate,[10] and in one prior enantioselective synthesis.[11] Reduction of (−)-**7** gave the amino alcohol **8**, (95%) which was converted to the *N*-methyl compound **10** (69% overall) by reduction of the benzyloxycarbonyl derivative **9**. Direct oxida-



Scheme 3 *Reagents and conditions*: i, H_2, $Pd(OH)_2$/C, MeOH; ii, $ClCO_2Bn$, Na_2CO_3, acetone; iii, $LiAlH_4$, THF, reflux; iv, $(Bu^tOCO)_2O$, $EtNPr^i_2$, CH_2Cl_2; v, PCC, CH_2Cl_2; vi, TFA, then Na_2CO_3 aq; vii, BzCl, pyridine, CH_2Cl_2

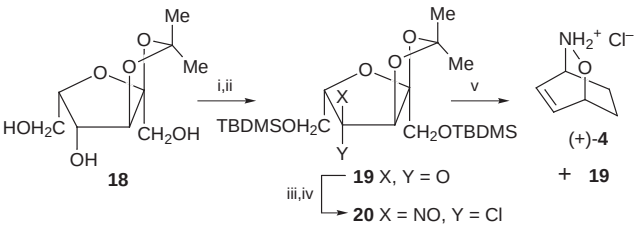
tion of **10** with Jones' reagent[10] gave (−)-**13**, but the isolation of the product in good yield was troublesome and the sequence shown in Scheme 3, involving protection of the basic nitrogen, gave (−)-**13** {$[\alpha]_D$ −50.0 (*c* 0.46, CH_2Cl_2)}§ in higher overall yield. Benzoylation of (−)-**13** gave the crystalline *N*-benzoyl derivative (−)-**14**, $[\alpha]_D$ −79.4 (*c* 0.97, CH_2Cl_2) {lit. for the enantiomer, $[\alpha]_D$ +78.0 (*c* 0.44, $CHCl_3$),[11] $[\alpha]_D$ +95.6 (*c* 1.3, $CHCl_3$)[9c]}.

The potent non-opioid analgesic activity shown by (−)-epibatidine [(−)-**17**], isolated from the poison frog *Epipedobates tricolor*, has led to many syntheses,[12] including some enantioselective approaches.[13] The availability of essentially enantiomerically pure cycloadduct (−)-**4** permitted a formal synthesis of (+)-epibatidine [(+)-**17**] (Scheme 4). Reductive cleavage of the N–O bond, and reaction with di-*tert*-butyl dicarbonate gave **15** (67%), and benzoylation of this gave (−)-**16**, mp 78–79 °C, $[\alpha]_D$ −87.6 (*c* 0.89, CH_2Cl_2), enantiomeric with an intermediate {mp 78–79 °C, $[\alpha]_D$ +86.6 (*c* 1.26, CH_2Cl_2)} used, *via ent*-**15**, in Trost and Cook's synthesis of (−)-epibatidine.[13b]



Scheme 4 *Reagents and conditions*: i, Zn, AcOH; ii, $(Bu^tOCO)_2O$, Na_2CO_3, acetone–MeOH; iii, BzCl, DMAP, pyridine, CH_2Cl_2

Although the use of a chiral auxiliary derived from D-xylose leads in both the above syntheses to the enantiomers of the natural products, the commercial availability of L-xylose makes it possible to employ identical chemistry in either enantiomeric series. However, L-xylose is relatively expensive, and so we have prepared (Scheme 5) a chloronitroso compound **20** pseudoenantiomeric with **2** from the cheap L-sorbose, *via* the



Scheme 5 *Reagents and conditions*: i, TBDMSCl, Et_3N, DMF; ii, PCC, mol. sieves, CH_2Cl_2; iii, $NH_2OH{\cdot}HCl$, $NaHCO_3$, EtOH–H_2O; iv, Bu^tOCl, CH_2Cl_2, 0 °C; v, cyclohexa-1,3-diene, $CHCl_3$–Pr^iOH–H_2O (100:100:1), 0 °C

monoisopropylidene compound **18**,[14] prepared using the same procedure as for the equivalent xylose derivative.[7]

When **20** was treated with cyclohexa-1,3-diene in the presence of water, the cycloadduct (+)-**4** was isolated in 76% yield, together with ketone **19** (86%). The ee of (+)-**4** was estimated as ⩾97% by derivatization with (+)-camphor-10-sulfonyl chloride.[4a] It thus appears that the two ketones **1** and **19** can be used to gain ready access to the two enantiomeric series through cycloadditions of the pseudoenantiomeric chloronitroso compounds **2** and **20**.

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Notes and References

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‡ The analogous chloronitroso compound derived from di-*O*-isopropylidene-D-glucose behaved very similarly to **2** in the reactions of both Schemes 1 and 2.

§ The specific rotation of physoperuvine does not seem to have been previously reported. Small negative values have been reported for the *hydrochloride* of both natural {$[\alpha]_D$ −0.8 (*c* 1.0, MeOH)} [ref. 9(*b*)] and synthetic {$[\alpha]_D$ −0.98 (*c* 1.28, MeOH)} (ref. 11) *S*-physoperuvine, although a small positive value has also been quoted in a different solvent {$[\alpha]_D$ +1.2 (*c* 1.3, H_2O)} [ref. 9(*a*)]. Our results imply that natural (*S*)-physoperuvine, as the free base, is significantly dextrorotatory.

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