

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.

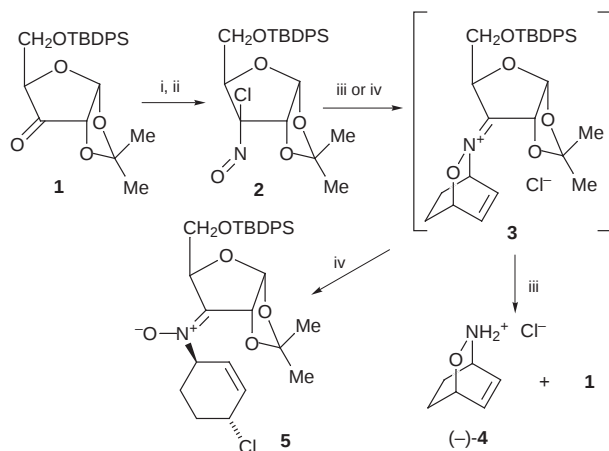
There has been considerable interest in recent years in the development of asymmetric versions of the hetero-Diels–Alder cycloaddition¹ of dienes with C-nitrosocompounds to form 3,6-dihydro-1,2-oxazines, since the further manipulation of the initial cycloadducts can be used to prepare a wide range of 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 auxiliaries⁶ 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

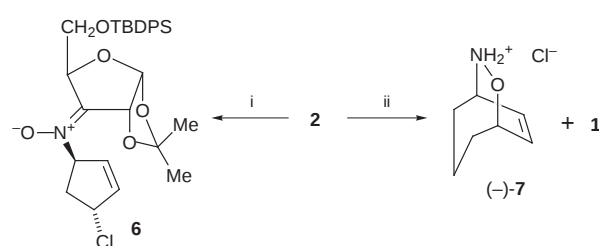
occurred from the *exo*-face was confirmed by X-ray crystallography, which also indicated the eclipsed nature of the chloronitroso unit⁸ (dihedral angle Cl–C–N–O, 0.8°).

Treatment of **2** with cyclohexa-1,3-diene in CHCl₃–PrⁱOH 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 (CHCl₃), only the nitron **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 nitron **6** (93% in CHCl₃), 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** {[α]_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 $\geq 96\%$. 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.

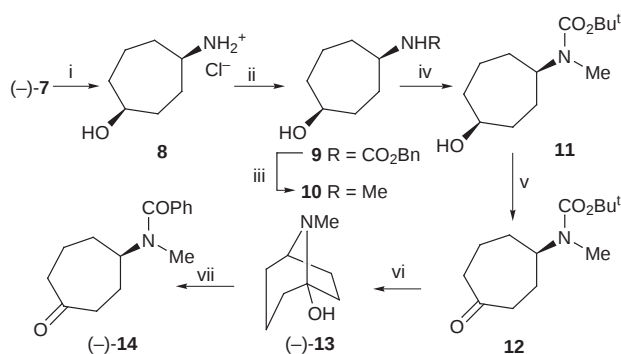


Scheme 1 Reagents and conditions: i, NH₂OH·HCl, NaHCO₃, EtOH–H₂O; ii, Bu^tOCl, CH₂Cl₂; iii, cyclohexa-1,3-diene, CHCl₃–PrⁱOH–H₂O (100:100:1), 0 °C; iv, cyclohexa-1,3-diene, CHCl₃, 0 °C



Scheme 2 Reagents and conditions: i, cyclopentadiene, CHCl₃, room temp; ii, cyclohepta-1,3-diene, CHCl₃–PrⁱOH–H₂O (100:100:1), 4 °C

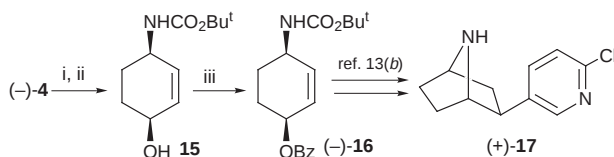
The cycloadduct (–)-**7** was used in an enantioselective synthesis of (–)-(*R*)-physoperuvine [(–)-**13**] (Scheme 3), the *S*-enantiomer of which is the major alkaloid of *Physalis peruviana* Linne.⁹ Physoperuvine has been synthesized as a racemate,¹⁰ and in one prior enantioselective synthesis.¹¹ 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 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH ; ii, ClCO_2Bn , Na_2CO_3 , acetone; iii, LiAlH_4 , THF , reflux; iv, $(\text{Bu}^t\text{OCO})_2\text{O}$, EtNPr_2 , CH_2Cl_2 ; v, PCC , CH_2Cl_2 ; vi, TFA , then Na_2CO_3 aq; vii, BzCl , pyridine, CH_2Cl_2

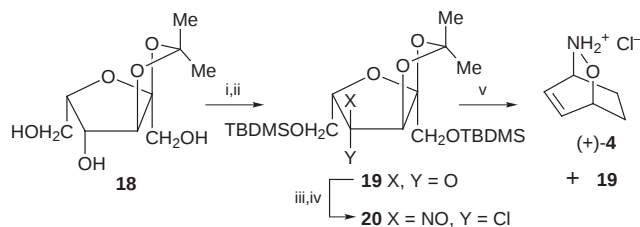
tion of **10** with Jones' reagent¹⁰ gave **(-)-13**, but the isolation of the product in good yield was troublesome and the sequence shown in Scheme 3, involving protection of the basic nitrogen, gave **(-)-13** $\{[\alpha]_{\text{D}} -50.0$ (c 0.46, $\text{CH}_2\text{Cl}_2\}$ § in higher overall yield. Benzoylation of **(-)-13** gave the crystalline *N*-benzoyl derivative **(-)-14**, $[\alpha]_{\text{D}} -79.4$ (c 0.97, CH_2Cl_2) [lit. for the enantiomer, $[\alpha]_{\text{D}} +78.0$ (c 0.44, CHCl_3),¹¹ $[\alpha]_{\text{D}} +95.6$ (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, $[\alpha]_{\text{D}} -87.6$ (c 0.89, CH_2Cl_2), enantiomeric with an intermediate {mp 78–79 °C, $[\alpha]_{\text{D}} +86.6$ (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, $(\text{Bu}^t\text{OCO})_2\text{O}$, 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, $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaHCO_3 , $\text{EtOH}\text{--}\text{H}_2\text{O}$; iv, Bu^tOCl , CH_2Cl_2 , 0 °C; v, cyclohexa-1,3-diene, $\text{CHCl}_3\text{--}\text{Pr}^i\text{OH}\text{--}\text{H}_2\text{O}$ (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 $\geq 97\%$ 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 $\{[\alpha]_{\text{D}} -0.8$ (c 1.0, $\text{MeOH}\}$ [ref. 9(b)] and synthetic $\{[\alpha]_{\text{D}} -0.98$ (c 1.28, $\text{MeOH}\}$ [ref. 11] *S*-physoperuvine, although a small positive value has also been quoted in a different solvent $\{[\alpha]_{\text{D}} +1.2$ (c 1.3, $\text{H}_2\text{O}\}$ [ref. 9(a)]. Our results imply that natural (*S*)-physoperuvine, as the free base, is significantly dextrorotatory.

- D. L. Boger and S. M. Weinreb, *Hetero-Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987; H. Waldman, *Synthesis*, 1994, 535; J. Streith and A. Defoin, *Synthesis*, 1994, 1107.
- e.g. J. Li, F. Lang and B. Ganem, *J. Org. Chem.*, 1998, **63**, 3403 and references cited therein; A. Ghosh and M. J. Miller, *Tetrahedron Lett.*, 1995, **36**, 6399 and references cited therein; S. F. Martin, M. Hartmann and J. A. Josey, *Tetrahedron Lett.*, 1992, **33**, 3583 and references cited therein; V. Gouverneur, G. Dive and L. Ghosez, *Tetrahedron: Asymmetry*, 1991, **2**, 1173; A. Defoin, A. Brouillard-Poichet and J. Streith, *Helv. Chim. Acta*, 1991, **74**, 103; V. Gouverneur and L. Ghosez, *Tetrahedron: Asymmetry*, 1990, **1**, 363; A. Miller and G. Procter, *Tetrahedron Lett.*, 1990, **31**, 1043.
- M. Sabuni, G. Kresze and H. Braun, *Tetrahedron Lett.*, 1984, **25**, 5377.
- (a) H. Braun, H. Felber, G. Kresze, F. P. Schmidtchen, R. Prewo and A. Vasella, *Liebigs Ann. Chem.*, 1993, 261; (b) A. Defoin, T. Sifferlen and J. Streith, *Synlett*, 1997, 1294.
- For amendment of an initially erroneous assignment of absolute configuration to the bicyclic adduct **4** see H. Braun, R. Charles, G. Kresze, M. Sabuni and J. Winkler, *Liebigs Ann. Chem.*, 1987, 1129.
- For a review on the use of sugar-based auxiliaries, see: P. G. Hultin, M. A. Earle and M. Sudharshan, *Tetrahedron*, 1997, **53**, 14823.
- J. Moravková, J. Capková and J. Stanek, *Carbohydr. Res.*, 1994, **263**, 61.
- A. Gieren and H.-J. Siebels, *Angew. Chem., Int. Ed. Engl.* 1976, **15**, 760.
- (a) M. Sahai and A. B. Ray, *J. Org. Chem.*, 1980, **45**, 3265; (b) A. B. Ray, Y. Oshima, H. Hikino and C. Kabuto, *Heterocycles*, 1982, **19**, 1233; (c) A. T. McPhail and A. R. Pinder, *Tetrahedron*, 1984, **40**, 1661.
- D. E. Justice and J. R. Malpass, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2559, and references cited therein.
- K. Hiroya and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 2205.
- N. S. Sirisoma and C. R. Johnson, *Tetrahedron Lett.*, 1998, **39**, 2059 and references cited therein; G. M. P. Giblin, C. D. Jones and N. S. Simpkins, *Synlett*, 1997, 589.
- (a) C. Szántay, Z. Kardos-Balogh, I. Moldvai, C. Szántay, Jr., E. Temesvári-Major and G. Blaskó, *Tetrahedron*, 1996, **52**, 11053; (b) B. M. Trost and G. R. Cook, *Tetrahedron Lett.*, 1996, **37**, 7485; (c) H. Kosugi, M. Abe, R. Hatsuda, H. Uda and M. Kato, *Chem. Commun.*, 1997, 1857; (d) S. Aoyagi, R. Tanaka, M. Naruse and C. Kibayashi, *Tetrahedron Lett.*, 1998, **39**, 4513.
- T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, 1934, **17**, 311.

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