ORGANIC LETTERS

2000
Vol. 2, No. 20
3165−3168

First Asymmetric Hetero Diels–Alder Reaction of 1-Sulfinyl Dienes with Nitroso Derivatives. A New Entry to the Synthesis of Optically Pure 1,4-Imino-L-ribitol Derivatives

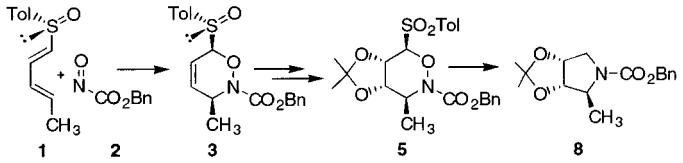
C. Arribas,[†] M. Carmen Carreño,*[,‡] José L. García-Ruano,*[,‡] Justo F. Rodríguez,[†] Mercedes Santos,[†] and M. Ascensión Sanz-Tejedor*[,†]

Departamento de Química Orgánica (E.T.S.I.I.), Universidad de Valladolid, Paseo del Cauce s/n, 47011, Valladolid, Spain, and Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

atejedor@dali.eis.uva.es

Received July 21, 2000

ABSTRACT



Hetero Diels–Alder (HDA) cycloaddition of chiral 1-*p*-tolylsulfinyl-1,3-pentadiene with benzyl nitrosoformate, under mild conditions, yields 2*H*-1,2-oxazine 3 with complete regioselectivity and π-facial diastereoselectivity. Sequential osmylation and protection of the resulting glycol gives the oxazine 5 which is directly transformed into enantiomerically pure 1,4,5-trideoxy-1,4-imino-L-ribitol 8 by reduction under Pd/C.

Optically pure 1-sulfinyl-1,3-butadienes have proved to be efficient chiral dienes in asymmetric Diels−Alder reactions[1] mainly due to their almost complete stereoselectivity control and to the easy evolution of their adducts through a highly stereocontrolled rearrangement.[2] Despite this, their use in asymmetric synthesis is strongly limited by their rather low reactivity even with good dienophiles. Our group has recently found that reactions of these dienes with heterodienophiles, such as 4-methyl-1,2,4-triazoline-3,5-dione, evolve under very mild conditions retaining the high stereoselectivity.[3] This result prompted us to investigate the usefulness of 1-sulfinyldienes in other asymmetric HDA reactions.[4] In this sense, our interest in the synthesis of monosaccharides and related compounds[5] drew our attention toward reactions with nitroso derivatives, because the adducts resulting from their reactions with 1-sulfinyldienes could be properly transformed into polyhydroxypyrrolidines according to the retrosynthetic sequence shown in Scheme 1.

[†] Universidad de Valladolid.
[‡] Universidad Autónoma de Madrid.

(1) Recent reviews: (a) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Gianneto, P. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1339. (b) García Ruano, J. L.; Cid, B. In *Topics in Current Chemistry*; Page, P. C. B., Ed.; Springer-Verlag: Berlin 1999; Vol. 204; pp 1−126.

(2) (a) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421. (b) Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1996**, *7*, 2151. (c) Carreño, M. C.; Cid, M. B.; García Ruano, J. L.; Santos, M. *Tetrahedron Asymmetry* **1997**, *8*, 2093. (d) Carreño, M. C.; Cid, M. B.; Colobert, F.; García Ruano, J. L.; Solladié, G. *Tetrahedron: Asymmetry* **1995**, *6*, 1439.

(3) Carreño, M. C.; Cid, B.; García Ruano, J. L.; Santos, M. *Tetrahedron Lett.* **1998**, *39*, 1405.

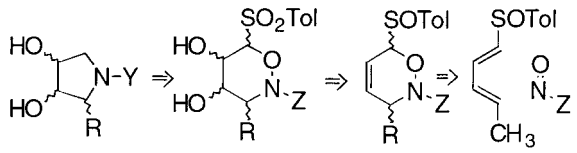
(4) For a recent review, see: Tietze L. F.; Kettschau. in *Topics in Curent Chemistry*; Metz, P., Ed.; Springer-Verlag: Berlin 1997; Vol. 189; p 4.

(5) For recent references, see: (a) Arroyo, Y.; López-Sastre, J. A.; Rodríguez, J. F.; Sanz-Tejedor, M. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2933. (b) Arroyo, Y.; López-Sastre, J. A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 973. (c) Arroyo, Y.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A. *Tetrahedron*: *Asymmetry* **2000**, *11*, 789.

(6) For reviews, see: (a) Elbein, A. D. *Am. Rev. Biochem.* **1987**, *56*, 497. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (c) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055. (d) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.

10.1021/ol0063611 CCC: $19.00
Published on Web 09/15/2000

Scheme 1



Glycosidase inhibitors have a large number of interesting potential applications including treatment of AIDS and diabetes as well as tumor metastasis inhibitors.[6] The interest of the polyhydroxypyrrolidines derives from the fact that they have been found to be potent inhibitors for many glycosidases.[7] Therefore, 5-methyl polyhydroxypyrrolidines with structures similar to that depicted in Scheme 1 have been recently proved to be efficient inhibitors of α-L-fucosidase.[8,9] The search for new methods for synthesizing these compounds with modified structure and configuration is of potential relevance.

The synthesis of polyhydroxylated pyrrolidines has been performed from naturally occurring chiral compounds (L-arabinopyranoside,[10] D-xilose,[11] D-gulono lactone,[12] D-glucose,[13] D-galactofuranose,[14] and L-lixopyranoside[15]) as well as enantiomer resolution[16] and asymmetric synthesis. Outstanding examples of the latter methodology mainly involve the use of enantiomerically pure chiral precursors controlling the formation of a new stereogenic center (from L-proline,[17] (*R*) and (*S*)-glutamic acid,[18] (+) and (−)-serine,[19] and (*R*)- or (*S*)-phenylglycinol[20]), but enzymatic catalysis[21] and asymmetric Diels−Alder reactions with nitrosodienophiles[22] have also been used. These cycloadditions have been extensively studied by Streith et al. in both racemic[23] and optically active series. Concerning these asymmetric cycloadditions, the best results have been obtained with chiral nitroso dienophiles,[9,24] whereas chiral dienes have been scarcely used since moderated asymmetric inductions are usually observed.[25] Thus, starting from a chiral *N*-dienyl lactam, Streith has synthesized a 3,4-dihydroxypyrrolidine.[25a]

With these precedents, our group has investigated the reaction of [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **1**[26] with benzyl nitrosoformate **2**. The highly reactive dienophile **2** was prepared in situ, in the presence of chiral diene **1**, by oxidation of the *N*-benzyloxycarbonyl hydroxamic acid with tetrabutylammonium periodate in CH_2Cl_2 solution.[27] Fortunately the reaction took place under very mild conditions (CH_2Cl_2, −78 to 0 °C). After 2 h, the ^{1}H NMR spectrum of the crude reaction revealed the existence of a 2:1 mixture of the 2*H*-1,2-oxazine **3** and the unreacted diene **1**. The addition of new portions of Bu_4NIO_4 and hydroxamic acid until complete disappearance of diene allowed to obtain compound **3** in 54% yield.[28]

No other diastereoisomers could be detected from the crude reaction by NMR, thus suggesting that both regioselectivity and stereoselectivity of the reaction are very high (Scheme 2).

(7) (a) *Iminosugars as Glycosidase Inhibitors-Nojirimycin and Beyond*; Stüzt, A. E., Ed., Wiley-VCH: Weinheim, 1999. (b) Bols, M. *Acc. Chem. Res*. **1998**, *31*, 1.

(8) (a) Liu, K. K.-C.; Kagimoto, T.; Pederson, L. R.; Zhong, Z.; Ichikawa, Y.; Porco, J. A.; Wong, Ch.-H. *J. Am. Chem. Soc*. **1991**, *113*, 6187. (b) Wong, Ch-H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Weston, B. W.; Lowe, J. B. *J. Am. Chem. Soc*. **1992**, *114*, 7321. (c) Quiao, L.; Murray, B. W.; Shimazaki, M.; Schultz, J.; Wong, Ch-H. *J. Am. Chem Soc*. **1996**, *118*, 7653.

(9) (a) Defoin, A.; Sifferlen, T.; Streith, J.; Dosbaâ, I.; Foglietti, M. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 363. (b) Sifferlen, T.; Defoin, A.; Streith, J.; Le Nouën, D.; Tarnus, C.; Dosbaâ, I.; Foglietti, M. J. *Tetrahedron* **2000**, *56*, 971.

(10) Reist, E. J.; Gueffroy, D. E.; Blackford, R. W.; Goodman, L. *J. Am. Chem Soc*. **1966**, *31*, 4025.

(11) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685.

(12) (a) Fleet, G. W. J.; Son, J. Ch. *Tetrahedron* **1988**, *44*, 2637. (b) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett*. **1993**, *34*, 7213. (c) Furneaux, R. H.; Limberg, G.; Tyler, P. C. *Tetrahedron* **1997**, *53*, 2915.

(13) (a) Han, S.-Y.; Lidlell, P. A.; Joullie, M. M. *Synth. Commun*. **1988**, *18*, 275. (b) Fleet, G. W. J.; Witty, D. R. *Tetrahedron*: *Asymmetry* **1990**, *1* 119. (c) Kayakiri, H.; Nakamura, K.; Takae, S.; Setoy, H.; Uchida, I.; Terano, H.; Hashimoto, M.; Tada, T.; Koda, S. *Chem. Pharm. Bull*. **1991**, *39*, 2807.

(14) Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thomson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 699.

(15) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 681.

(16) Witte, J. F.; McClard, R. W. *Tetrahedron Lett*. **1991**, *32*, 3927.

(17) (a) Guillerm, G.; Varkados, M.; Auvin, S.; Le Goffic, F. *Tetrahedron Lett*. **1987**, *28*, 535. (b) Goli, D. M.; Cheesman, B. V.; Hassan, M. E.; Lodaya, R.; Slama, J. T. *Carbohydr. Res*. **1994**, 219. (c) Blanco, M. J.; Sardina, F. J. *J. Org. Chem*. **1998**, *63*, 3411.

(18) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull*. **1990**, *38*, 2712.

(19) Huang, Y.; Dalton J. *J. Org. Chem*. **1997**, *62*, 372.

(20) (a) Meyers, A.; Andres, C. J.; Resek, J. E.; McLaughlin, M. A.; Wooddall, C.-C.; Lee, H. *J. Org. Chem*. **1996**, *61*, 2586. (b) Dudot, B.; Micouin, L.; Baussamne, I.; Royer, J. *Synthesis* **1999**, 688.

(21) (a) Ziegler, T.; Straub, A,; Effenberger, F. *Angew. Chem*. **1988**, *100*, 737. (b) Liu, K. K.-C.; Kagimoto, T.; Pederson, L. R.; Zhong, Z.; Ichikawa, Y.; Porco, J. A.; Wong, Ch.-H. *J. Am. Chem. Soc*. **1991**, *113*, 6678. (c) Liu, K. K.-C.; Kagimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, Ch.-H. *J. Org. Chem*. **1991**, *56*, 6280. (d) Wang, Y. F.; Dumas, D. P.; Wong, Ch.-H. *Tetrahedron Lett*. **1993**, *34*, 403.

(22) For reviews, see: (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107. (b) Streith, J.; Defoin, A. *Synlett* **1996**, 189.

(23) (a) Behr, J.-B.; Defoin, A.; Streith, J. *Heterocycles* **1994**, *37*, 747. (b) Behr, J.-B.; Defoin, A.; Mahmood, N.; Streith, J. *Helv. Chim. Acta* **1995**, *78*, 1166.

(24) Defoin, A.; Sifferlen, T.; Streith, J. *Synlett* **1997**, 1294.

(25) (a) Defoin, A.; Pires, J.; Streith, J. *Synlett* **1991**, 417. (b) Behr, J.-B.; Defoin, A.; Pires, J.; Streith, J.; Macko, L.; Zehnder, M. *Tetrahedron* **1996**, *52*, 3283. (c) Hussain, A.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 2123.

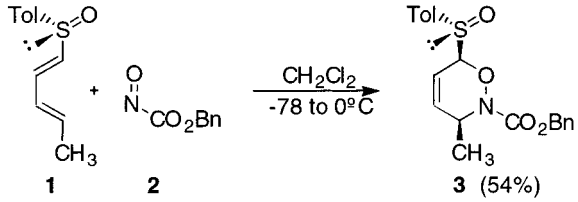
(26) Solladié, G.; Ruiz, P.; Colobert, F.; Carreño, M. C.; García-Ruano, J. L. *Synthesis* **1991**, 1011.

(27) (a) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Commun*. **1973**, 704. (b) Keck, G. E.; Fleming, St. A. *Tetrahedron Lett*. **1978**, 4763.

(28) To a solution of diene **1** (2.7 g, 13.00 mmol) and Bu_4NIO_4 (2.9 g, 6.00 mmol) in CH_2Cl_2 (20 mL, with ca. 50 beads of 4 Å molecular sieves) at −78 °C was added within 1 h, portionwise, hydroxamic acid (3.3 g, 19.00 mmol) in CH_2Cl_2 (10 mL). The mixture was warmed to 0 °C and stirred for 2 h. Then the mixture was cooled at −78 °C, and new portions of Bu_4NIO_4 (6.00 mmol) and hydroxamic acid (19.00 mmol) were added. After stirring for 2 h at 0 °C, the mixture was poured into CH_2Cl_2 (20 mL), washed with Na_2SO_3 (10%, 2 × 10 mL) and saturated $NaHCO_3$ (2 × 10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Et_2O:hexane, 3:1), to give [3*S*,6*R*,(*S*)*R*]-*N-benzyloxycarbonyl-3,6-dihydro-3-methyl-6-*(*p-tolylsulfinyl*)*-2H-1,2-oxazine* ***3*** as a white solid 2.6 g, 7.01 mmol, 54%); mp = 195 °C; $[\alpha]^{20}_D$ = +26.1° (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, *J* = 6.9, C**H**$_3$-C3), 2.40 (s, 3H, C**H**$_3$-C$_6$H$_4$), 4.41 (cddd, 1H, *J* = 1.3, 2.7, 4.4, 6.9, **H**-C3), 5.17, 5.23 (system AB, 2H, *J* = 12.2, PhC**H**$_2$-), 5.61 (ddd, 1H, *J* = 1.6, 1.3, 2.7, **H**-C6), 5.85 (ddd, 1H, *J* = 1.3, 1.3, 10.4, **H**-C5), 5.94 (ddd, 1H, *J* = 1.6, 4.4, 10.4, **H**-C4), 7.26−7.34 (m, 7H, C$_6$**H**$_5$- and -C$_6$**H**$_4$-), 7.60 (system AA′BB′, 2H, -C$_6$**H**$_4$-); ^{13}C NMR ($CDCl_3$) δ 17.9 (**C**H$_3$-C3), 21.3 (**C**H$_3$-C$_6$H$_4$), 51.1 (**C**3), 68.0 (Ph**C**H$_2$-), 89.6 (**C**6), 117.1 (**C**4), 125.9, 128.1, 128.4, 128.6, 129.3 (H**C**-arom), 133.7 (**C**5), 134.8, 135.5, 142.4 (**C**-arom), 155.1 (**C**=O).

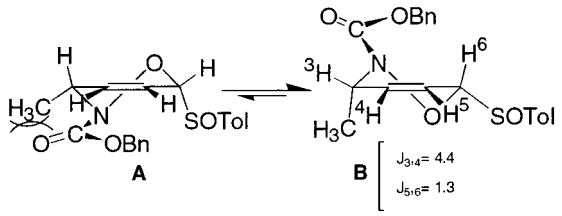
(29) This interaction, which is similar to the allylic strain, must also be responsible for the preferred axial orientation of the phenyl group (bulkier than the methyl one) in *N*-alkoxycarbonyl derivatives of 3-phenyl 1,4-thiazanes (García Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H.; Olefirowicz, E. M.; Eliel, E. L. *J. Org. Chem*. **1992**, *57*, 4215).

Scheme 2



Structurally significant ^{1}H NMR parameters of compound **3** are depicted in Scheme 3. Vicinal coupling constants $J_{3,4}$

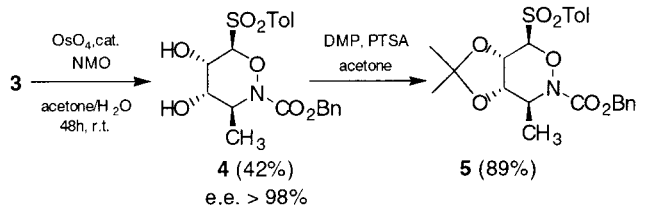
Scheme 3



(4.4 Hz) and $J_{5,6}$ (1.3 Hz) are consistent with the relative pseudoequatorial and pseudoaxial arrangements for H-3 and H-6, thus suggesting that the conformation **B** is the favored one. This conformational preference can be explained by assuming the conjugation of the nitrogen with the alkoxy carbonyl group. This fact determines that the interactions of their oxygens with the almost eclipsed equatorial substituents at C-3[29] shift the conformational equilibrium toward **B**, displaying the methyl group in axial orientation, thus forcing the *p*-tolylsulfinyl group to adopt an equatorial arrangement. This would explain the low tendency of compound **3** to give the sulfoxide−sulfenate rearrangement (it requires the axial arrangement of the sulfinyl group) in contrast with other adducts derived from 1-sulfinyldienes.[2,3]

Cis-dihydroxylation of adduct **3**, performed with catalytic amounts of OsO_4 in the presence of the *N*-methylmorpholine *N*-oxide, afforded diol **4** (42%) as the only diastereoisomer, along with a small amount of α,*β*-unsaturated lactame.[30] As can be seen, the sulfinyl group has been oxidized to sulfone in this process (Scheme 4). The optical purity of diol **4** is almost complete (>98% ee), as established by ^{1}H NMR studies of its (*R*)- and (*S*)-di-MPTA esters,[31] which revealed that both HDA cycloaddition and dihydroxylation have occurred with total *π*-facial selectivity. Diol **4** was trans-

Scheme 4



formed into its acetonide **5**[32] by treatment with DMP in PTSA (rt, 12 h, 89%).

The absolute configuration of compound **5** was unequivocally assigned as S_3,S_4,S_5,R_6 by X-ray analysis[33] (Figure 1). On the basis of this assignment the absolute configuration of diol **4** and cycloadduct **3** can be established.

The stereochemical course of the HDA reaction can be explained by considering that the heterodienophile approaches to the less hindered face of diene—the one that

(30) A small amount (18%) of *N*-benzyloxycarbonyl 5-methylpyrrolin-2(5*H*)-one was also isolated. Its formation from **3** can be rationalized according to a similar evolution to that described for Firl and Kresce for other oxazine derivatives bearing electron-withdrawing groups at C-6, which are transformed into pyrrolinone derivatives by treating with base (Firl, J.; Kresce, G. *Chem. Ber.* **1966**, *99*, 3695. Defoin, A.; Geffroy, G.; Le Nouen, D.; Spileers, D.; Streth, J. *Helv. Chim. Acta* **1988**, *71*, 1642).

(31) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 125.

(32) [3*S*,4*S*,5*S*,6*R*]-*N-Bencyloxycarbonyl-3,4,5,6-tetrahydro-4,5-dihidroxy-3-methyl-6-(p-tolylsulfonyl)-1,2-oxazine* ***4***: syrup, $[\alpha]^{20}_D = -16.8°$ (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 1.31 (d, 3H, *J* = 7.3, C**H**$_3$-C3), 2.43 (s, 3H, C**H**$_3$-C$_6$H$_4$), 2.85 and 3.78 (2s, each 1H, O**H**-C4, O**H**-C5) (exchangeable with D_2O), 3.97 (dd, 1H, *J* = 2.7, 2.7, **H**-C4), 4.46−4.50 (m, 2H, **H**-C5 and **H**-C3); 5.01−5.11 (m, 3H, PhC**H**$_2$- and **H**-C6), 7.26−7.34 (m, 7H, C$_6$**H**$_5$- and -C$_6$**H**$_4$-), 7.8 (system AA′BB′, 2H, -C$_6$**H**$_4$-); ^{13}C NMR ($CDCl_3$) *δ* 13.9 (**C**H$_3$-C3), 21.8 (**C**H$_3$-C$_6$H$_4$-), 56.3 (**C**3), 62.8 y 69.4 (**C**4, **C**5), 67.9 (Ph**C**H$_2$-), 89.1 (**C**6), 128.0, 128.2, 128.4, 129.1 y 129.7 (H**C**-arom), 132.8, 135.4, 145.9 (**C**-arom), 156.1 (**C**═O). EM (*m*/*q*) (id, ie): 422 (100%, M + 1), 378 (84, $C_{19}H_{21}NO_5S^+$), 222 (37, $C_6H_8NO_6S^+$), 157 (19, $C_6H_7NO_4^+$). [3*S*,4*S*,5*S*,6*R*]-*N-Benzyloxycarbonyl-3,4,5,6-tetrahydro-3-methyl-4, 5-(dimethylmetilendioxy)-6-(p-tolylsulfonyl)-1,2-oxazine* ***5***: white solid; T_f = 143 °C; $[\alpha]^{20}_D = +13.3°$ (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 1.35 and 1.36 (2s, each 3H, C(C**H**$_3$)$_2$), 1.35 (d, 1H, *J* = 7.2, C**H**$_3$-C3), 2.43 (s, 3H, C**H**$_3$-C$_6$H$_4$), 4.16 (dd, 1H, *J* = 1.1, 5.0, **H**-C4), 4.61 (cd, 1H, *J* = 1.1, 7.2, **H**-C3), 4.74−4.81 (m, 2H, **H**-C5, **H**-C6), 4.90, 5.00 (system AB, 2H, *J* = 12.0, PhC**H**$_2$-), 7.19−7.34 (m, 7H, -C$_6$**H**$_5$ and -C$_6$**H**$_4$-), 7.83 (system AA′BB′, 2H, -C$_6$**H**$_4$-); ^{13}C NMR ($CDCl_3$) *δ* 15.6 (**C**H$_3$-C3), 21.8 (**C**H$_3$-C$_6$H$_4$), 26.0 and 27.8 (**C**(**C**H$_3$)$_2$), 52.0 (**C**3), 66.7 and 74.9 (**C**4, **C**5), 68.1 (Ph**C**H$_2$-), 90.7 (**C**6), 110.9 (**C**(CH$_3$)$_2$), 128.3, 128.4, 128.5, 129.3, 129.7 (H**C**-arom), 133.4, 135.3, 145.5 (**C**-arom), 155.4 (**C**═O). EM (*m*/*q*) (id, ie): 462 (100%, M + 1), 418 (64, $C_{20}H_{20}NO_7S^+$), 290 (21; $C_{15}H_{17}NO_5S^+$), 200 (20, $C_9H_{14}NO_4^+$), 171 (56, $C_8H_{13}NO_3^+$), 156 (69, $C_7H_8SO_2^+$). HMRS calcd for $C_{23}H_{28}NO_7S$ 462.158649, found 462.157129.

(33) Crystal structure analysis of **5** ($C_{23}H_{27}NO_7S$): orthorhombic, space group *P*212121; *a* = 8.776 (15), *b* = 15.118 (3), *c* = 17.358 (3) Å; *V* = 2303.1 (7) Å^3; *Z* = 4; ρ_{calcd} = 1.366 mg/m^3. Crystals were obtained by slow difussion of hexane into concentrated solution of **5** in Et_2O at rt. Crystal size: 0.26 × 0.2 × 0.2 mm^3. Theta range: 1.79 to 23.32°. μ(Mo Kα mm^{-1}) = 0.19. *T* = 573 K. Reflections collected: 12752. Independent reflections: 3332 (R_{int} = 0.0505). Refinement method full-matrix least squares on F^2. Data/restraints/parameters = 3332/0/293. Goodness-of-fit on F^2 = 0.902. Final *R* indices [$I>2\sigma(I)$]: R1 = 0.0312, wR2 = 0.0610. R indices (all data) R1 = 0.0462, wR2 = 0.0656. Absolute structure parameter = 0.09-(7). Largest diff. peak and hole: 0.106 and 0.135 e Å^{-3}.

(34) *([2R,3S,4S]-N-Benzyloxycarbonyl-1,4,5-tridesoxy-1,4-imine-2,3-O-isopropylidene-L-ribitol)* ***8***: syrup; $[\alpha]^{20}_D = +36.6°$ (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, rt) *δ* 1.10 and 1.16 (2d, each 3H, *J* = 6.9, CH$_3$-C2 I and II), 1.30 (s, 6H, C(CH$_3$)$_2$), 1.43 (s, 6H, C(CH$_3$)$_2$), 3.45 (dd, 2H, *J* = 5.2, 12.9, H.-C5), 3.84 and 3.91 (2d, each 1H, *J* = 12.9, H′-C5 I and II), 4.19 and 4.24 (2c, each 1H, *J* = 6.9, H.-C2 I and II), 4.38 (d, 2H, *J* = 5.8, H.-C3), 4.75 (dd, 2H, *J* = 5.2, 5.8, H.-C4), 5.10, 5.18 (sist. AB, 4H, *J* = 12.3, PhCH$_2$−), 7.30−7.37 (m, 10H, -C$_6$H$_5$); ^{13}C NMR($CDCl_3$) *δ* 16.3 and 17.0 (CH$_3$-C2 I and II), 24.8 and 26.8 (C(CH$_3$)$_2$), 50.7 and 50.9 (C5 I and II), 58.9 and 59.2 (C2 I and II), 66.8 (PhCH$_2$−), 85.1 and 85.8 (C4, C3), 111.7 (C(CH$_3$)$_2$), 127.7, 127.9, 128.4 (HC-arom), 138.8 (C-arom), 155.4 and 157.5 (C═O). EM (*m*/*q*) (id, ie): 291 (12.76%, M$^+$), 276 (16.07, M − CH$_3$), 91 (100, $C_7H_7^+$). HRMS (EI) calcd for $C_{16}H_{21}NO_4$ 291.147058, found 291.146580. Restricted rotation around the N−CO$_2$Bn bond determines that the ^{1}H NMR signals corresponding to Me-C2, H-C5, and H-C2 appear as a serie of two sets of same intensity signals when the spectrum is registered at temperature below 50 °C.

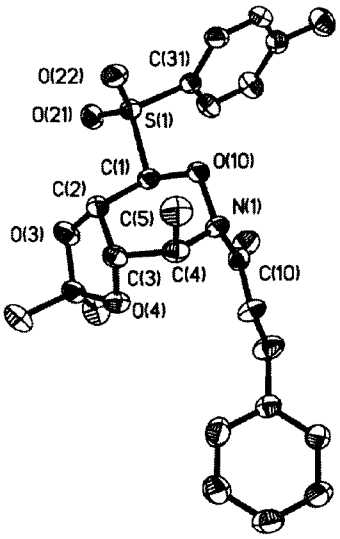


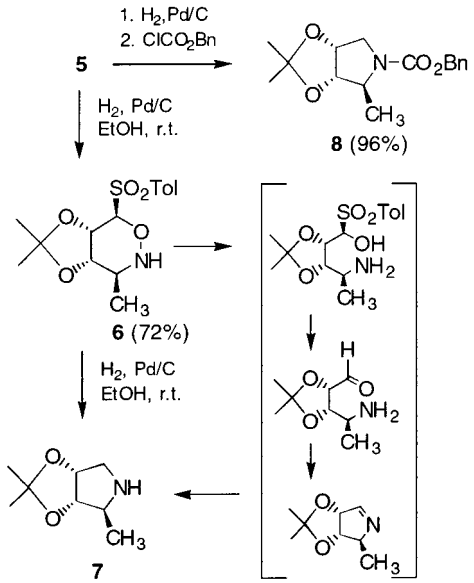
Figure 1. Structure of **5** in the crystal.

supports the lone electron pair at sulfur—with the sulfinyl group in a s-*trans* arrangement with respect to C(1)═C(2). The same approach has also been suggested to explain the results obtained in other 1-sulfinyl diene reactions with dienophiles such as *N*-methylmaleimide and maleic anhydride,[2] or heterodienophiles as 4-methyl-1,2,4-triazoline-3,5-dione.[3] In these cases, electrostatic repulsion between the carbonyl and sulfinyl oxygens in the transition structure was invoked to justify the higher reactivity of the s-*trans* conformation of the sulfinyl oxygen. However, the fact that such a conformation was also required to explain the results of the nitroso derivatives suggests it could be highly preferred (or the most reactive one) for 1-sulfinyl dienes, regardless of the possible interactions present in the transition structure with other groups present at dienophiles and heterodienophiles. The reasons for this preference are not easily understandable.

Concerning the stereochemical course observed for the *cis*-hydroxylation step, the attack of the reagent from the opposite face of the double bond to that containing the methyl and SOTol groups (see Scheme 4) must be clearly favored from a steric point of view.

The transformation of the 1,2-oxazine **5** into pyrrolidine **7** was performed with H_2 in the presence of Pd/C as the catalyst (rt, 1 h). Hydrogenolysis of the benzyl residue followed by decarboxylation of the resulting carbamic acid afforded 1,2-oxazine **6**, which can be isolated in 72% yield. Subsequent reaction of this compound with the reducing agent afforded directly pyrrolidine **7**. This can be explained by assuming that hydrogenolysis of the N—O bond, removal of the sulfonyl moiety with formation of an unstable aminoaldehyde, cyclization to the corresponding pyrroline derivative, and final reduction of the C═N have taken place in only one synthetic step (Scheme 5).

Scheme 5



As dihydroxypyrrolidine **7** is difficult to purify (isolated yield 23%), it was characterized as its *N*-benzyloxycarbonyl derivative **8**.[34] Finally we have found reaction conditions that allow a one-pot transformation of **5** into **8**. Hydrogenolysis of **5** for 8 h at rt, followed by treatment with benzyl chloroformate in aqueous $NaHCO_3$ (0 °C, 1 h), afforded dihydroxypyrrolidine **8** in 96% yield.

In summary, we have reported the first asymmetric HDA reaction of 1-sulfinyldienes with acylnitroso derivatives. Diene **1** evolves with benzyl nitrosoformate under very mild conditions (contrasting with the low reactivity exhibited with homodienophiles) with complete regioselectivity and stereoselectivity to afford enantiomerically pure 2*H*-1,2-oxazine **3**. Dihydroxylation followed by hydrogenolysis of the *N*-benzyloxycarbonyl 6-sulfonyl-1,2-oxazine ring provides an easy new access to optically pure dihydroxypyrrolidines. In this paper we have applied this sequence to prepare compound **8**. The use of different 1-sulfinyldienes, as well as the application of other dihydroxylation procedures, to obtain a variety of dihydroxypyrrolidines, are currently in progress.

Acknowledgment. We thank the DGICYT (Grants PB98-0078) and JCYL (VA07/00B) for financial support. We thank Dr. Daniel Miguel for structural elucidation.

OL0063611