Total Synthesis of Optically Active *N*-Benzoyldaunosamine from an Azetidinone

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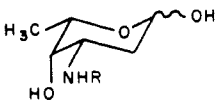
The azetidinone adduct **5** formed from chlorosulfonyl isocyanate and (*E*)-1,3-pentadiene was employed as a key intermediate to accomplish an efficient synthesis of optically active L$_s$-*N*-benzoyldaunosamine (**1b**).

Introduction

Daunosamine (**1a**), which has the L$_s$-*lyxo* configuration, is the glycosidic moiety of the therapeutically useful anthracycline antibiotics daunorubicin and adriamycin.[2] As such, it has been the object of intense synthetic study, and while both chiral[3,4] and racemic[5] routes have been described, the majority have focused on methods for preparing the optically active compound.



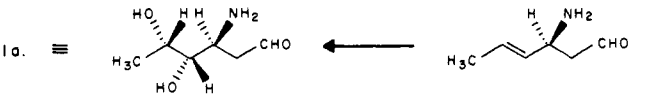
1a. R = H
1b. R = COC$_6$H$_5$

A variety of chiral starting materials have been employed in these studies. Marsh et al.[3] accomplished the first total synthesis of optically active daunosamine (**1a**) from L-fucose. Procedures from less expensive D sugars[3b] were subseqently developed; however, these sequences were longer. Fermentation intermediates,[3e] D-threonine and tartaric acid[3f,b] have also been employed as precursors.

Dyong and Weiman[3g] reported the first use of asymmetric induction to accomplish a chiral total synthesis of daunosamine. Another novel chiral total synthesis of **1a** from achiral precursors was reported by Wovkulich and Uskokovic.[3h] In this preparation, asymmetric induction was achieved through intramolecular cyclization of a nitrone intermediate prepared from an optically active hydroxylamine.

Recently, we communicated the development of a brief, high yield route for diastereoselective preparation of racemic *N*-benzoyldaunosamine ((±)-**1b**)[5d] based on the novel use of the propenylazetidinone **5** as an intermediate. In this paper we describe the details of that study and its further development as a route for synthesis of optically active *N*-benzoyldaunosamine (L$_s$-**1b**).

The small number of asymmetric centers in daunosamine (**1a**) initially prompted us to consider its total synthesis from simple starting materials. Examination of the Fischer projection of the acyclic form of daunosamine indicated that cis hydroxylation of the *E* olefinic precursor **2** on the face anti with respect to the amide would lead



2.

to a product with both the correct pattern of functionalization and stereochemical relationships. Although there were no published studies on the stereochemistry of hydroxylation of acyclic allyl amide systems,[7] we expected that an amide and a bulky cis-hydroxylating reagent such as osmium tetraoxide would cooperatively function to favor anti hydroxylation.

The similarity of **2** to the azetidinone adduct **5**, the sole regioisomer of $_\pi2_a + _\pi2_s$ cycloaddition[8] of chlorosulfonyl isocyanate (**4**) with (*E*)-1,3-pentadiene (**3**), was apparent, and a synthetic plan utilizing **5** was developed. The conceptual simplicity of this approach, which is shown in Scheme I, and the commercial availability of the starting materials led us to test the experimental validity of this approach.

Cycloaddition of chlorosulfonyl isocyanate (**4**) to (*E*)-1,3-pentadiene (**3**) was performed as previously described.[8] Without isolation and in the same pot, the *N*-chlorosulfonyl moiety was reductively cleaved with sodium sulfite[9] to furnish the propenylazetidinone **5** in less than 25% yield. The origin of the modest yield was ultimately traced to the reductive cleavage of the *N*-chlorosulfonyl residue. Careful control of the temperature during this step raised the yield of **5** to a respectable 72%.

Methanolysis of the azetidinone **5** (CH_3OH, HCl, 2 h, room temperature) cleaved the β-lactam and gave the methyl ester amine hydrochloride **6a** (~100%) as colorless needles after recrystallization. In order to provide both steric bulk and protection for the amine group, **6b** was converted to the benzamide derivative **6c** (ArCOCl, py, CH_2Cl_2; 80%).

(1) Recipient of a Career Development Award, 1978–1983, from the National Cancer Institute (CA 00486).

(2) Structure and absolute configuration: Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335.

(3) L$_s$-Daunosamine and derivatives: (a) Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1967**, 973. (b) Horton, D.; Weckerle, W. *Carbohyd. Res.* **1975**, *44*, 227. (c) Yamaguchi, T.; Kojima, M. *Ibid.* **1977**, *46*, 343-350. (d) Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1031. (e) Fronza, G.; Fuganti, C.; Grasselli, P.; *Ibid.* **1980**, 442. (f) Fuganti, C.; Grasselli, P.; Fantoni, P. *Tetrahedron Lett.* **1981**, 4017. Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Ibid.* **1979**, 7883. Fuganti, C.; Grasselli, P.; Giuseppe, P. D. *J. Org. Chem.* **1983**, *48*, 909. (g) Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 2666. (h) Wovkulich, P. M.; Uskovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (i) Grethe, G.; Mitt, T.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5309. (j) Grethe, G.; Sereno, J.; Williams, T. H.; Uskokovic, M. R. *Ibid.* **1983**, *48*, 5315.

(4) D$_t$-Daunosamine and derivtives: (a) Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1965**, 627;*Carbohyd. Res.* **1967**, *4*, 422. (b) Baer, H. H.; Capek, K.; Cook, M. C. *Can. J. Chem.* **1969**, *47*, 89.

(5) (a) Wong, C. M.; Ho, T.-L.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144. (b) Dyong, I.; Weimann, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 682. (c) Iwataki, I.; Nakamura, Y.; Takahashi, K. Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. (d) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227. (e) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686.

(6) The synthesis of racemic **1a** reported by DeShong and Leginus[5e] can formally be considered a route for preparation of optically active **1a** since the aldehyde precursor has been prepared from tartaric acid.[3f]

(7) While our work was in progress, Dyong and Wiemann[3g] reported the hydroxylation of an allyl tosylamide with osmium tetraoxide.

(8) Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, *36*, 2841. Goebel, P.; Claus, K. *Liebigs Ann. Chem.* **1969**, *722*, 122.

(9) Durst, T.; O'Sullivan, M. J. *J. Org. Chem.* **1970**, *35*, 2043.

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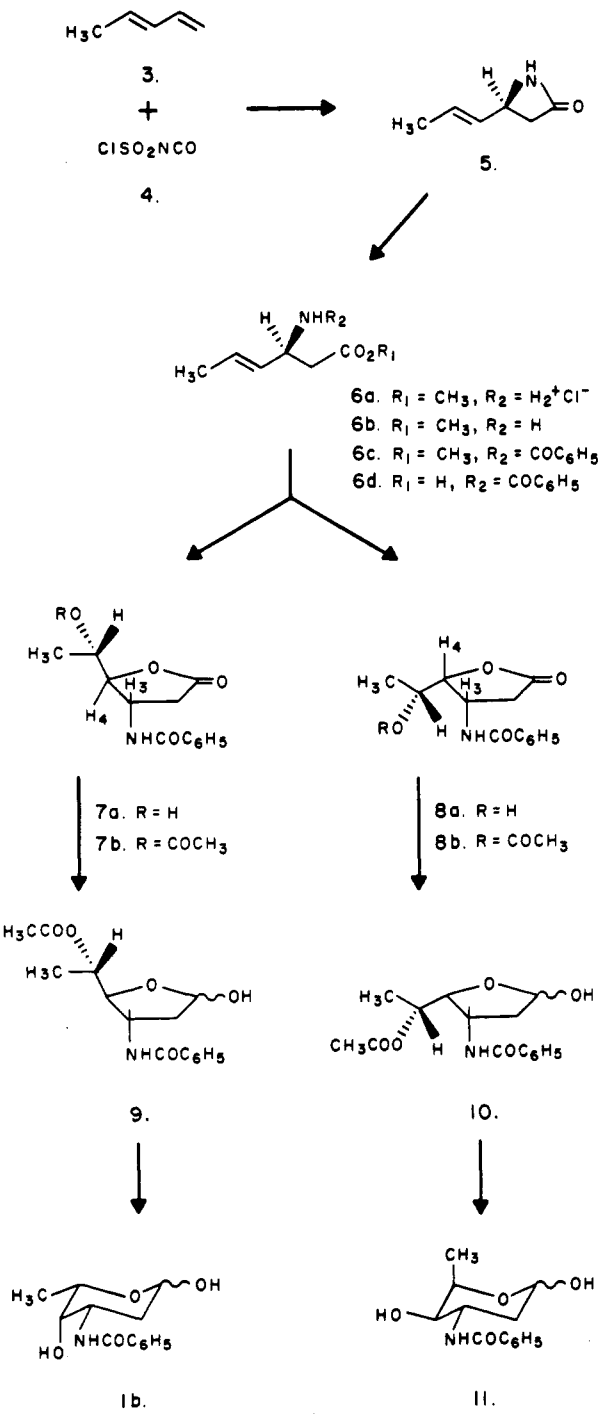
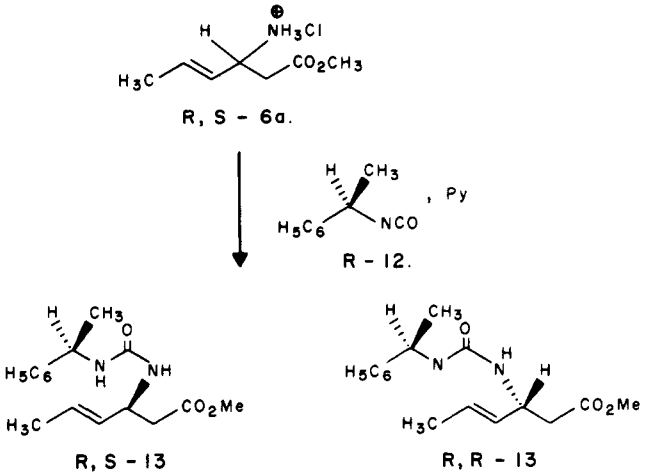
Scheme I



Scheme II



Cis hydroxylation of the olefinic entity in **6c** using a catalytic amount of osmium tetraoxide with trimethylamine *N*-oxide (TMNO)[10-12] directly furnished the lactones **7a** and **8a** (91% yield) in a 62:38 ratio[13-15] based on isolated material and substantiated by integration of the methyl doublets in the ^{1}H NMR spectrum. Both large (>20-g) and small (1-g) scale separation of the isomers was readily achieved through recrystallization; however, the efficiency was low. Small scale separations were conveniently performed by chromatography. For large scale hydroxylations, the pure *lyxo* isomer **7a** was obtained through crystallization of the initial product followed by a single recrystallization (38%). Partial evaporation of the filtrate and collection of the resultant crystals followed by recrystallization gave the pure *xylo* isomer **8a** (26%). The combined filtrates were then chromatographed to complete the separation.

The chemical shifts of the protons in the ^{1}H NMR spectra of the individual lactone isomers were well separated and decoupling experiments permitted straightforward assignment of the structures. Since the dihedral angle between coupling protons in trans-3,4-disubstituted γ-lactones approaches 90°,[18] the isomer **7a** exhibiting the smaller coupling constant[19] between H_3 and H_4 (J = 3.52 Hz at 4.39 ppm) was assigned the trans geometry and *lyxo* configuration. Conversely, the isomer **8a** exhibiting the larger coupling constant (J = 7 Hz at 4.38 ppm) between H_3 and H_4 was assigned the cis geometry and *xylo* configuration.

Partial reduction of the lactone moiety in **7a** and **8a** to afford the corresponding amino sugars proved unexpectedly difficult. Reaction of either lactone isomer with sodium borohydride in ethanol gave the corresponding triol from overreduction as the major product. Treatment of the hydroxy lactones with DIBAL in toluene (−78 °C) also gave considerable triol product; however, a substantial amount of starting material was reclaimed. The low solubility of the hydroxy lactones in toluene was recognized as the probable cause for both overreduction and the lack

(10) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449.
(11) When *N*-methylmorpholine *N*-oxide was employed as the oxidant (VanRheenen, V.; Kelly, R. C.; Chu, D. Y. *Tetrahedron Lett.* **1976**, 1973), a substantial amount of uncyclized diol ester intermediate was produced.
(12) The use of pyridine, common in osmium tetraoxide hydroxylations, was found to be detrimental. In addition, the reactions were significantly slower.
(13) Kishi[16] and Stork[17] and their co-workers have reported a study of the osmium tetraoxide hydroxylation of allyl alcohols and their derivatives and have suggested that osmate addition occurs on the least hindered face of the olefin in a conformation where the hydrogen bound to the allyl carbon is in the same plane as the olefinic carbons. Our results are in agreement with their proposal. We also emphasize that the osmium tetraoxide reagent does not complex with either the alcohol groups they studied or with the amide functionality present in our work.
(14) Dyong et al.[3g] have reported that osmium tetraoxide hydroxylation of an allyl tosylamide system to **6c** gave an 80:20 ratio of anti to syn diol products. They suggest this selectivity results from a coiled conformer that hinders attack on one face of the olefin. We suggest instead that the reactive conformer is that suggested by Kishi and Stork and that the observed differences in product ratios obtained by their laboratories and ours are due to the larger steric volume of the tetrahedral tosylamide group compared with an essentially planar benzamide functionality.
(15) We have recently found an example of a stereospecific hydroxylation by osmium tetraoxide of an olefinic center in an acyclic system guided by a sulfoxide functionality more remote than homoallylic. Hauser, F. M.; Ellenberger, S. R. *J. Am. Chem. Soc.*, in press.
(16) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943, 3947.
(17) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.
(18) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc.* **1975**, 1480.
(19) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.

of reduction of the lactone carbonyl group. In order to increase their solubility, the hydroxy lactones **7a** and **8a** were converted to the acetates **7b** and **8b** that were soluble in THF. Reduction of the individual acetate derivatives **7b** and **8b** gave the corresponding acetoxy furanoses **9** and **10** in 75% and 58% yield. Ammonolysis of **9** and **10** quantitatively furnished DL-*N*-benzoyldaunosamine (**1b**) and the *xylo* isomer **11**, respectively.

In order to develop this same plan as a route to optically active *N*-benzoyldaunosamine (L$_s$-**1b**), resolution of an intermediate was necessary. Derivatives of the amine group in **6a** were initially examined since this functionality is directly attached to the asymmetric center. Reaction of **6a** with (*R*)-(+)-α-methylbenzyl isocyanate (**12**) gave the expected diastereoisomeric mixture of ureas (*RS*)-**13** and (*RR*)-**13** shown in Scheme II. Distinctly separate absorptions for the methoxy and vinyl methyl groups were observed in the ^{1}H NMR spectrum of the mixture. Chromatographic separation of the diastereoisomers was not possible; however, they were readily separated in pure form through recrystallization.

Numerous attempts to effect acid, base, or nitrous acid hydrolysis of the urea linkage to obtain the optically active amine were unsuccessful.[20] Furthermore, reduction of the amide to a formamidine residue with sodium borohydride[21] followed by hydrolysis was also futile. However, the urea derivatives proved most useful in subsequent resolution studies as an analytical method for determination of enantiomeric purity.

In further efforts to resolve an intermediate, salts of both the amine **6b** and acid **6d**[22] with optically active acids and bases (amines) were prepared. While salts of the acid **6d** provided little or no resolution, the D-tartrate salt of the amine **6b** resulted in partial resolution after numerous recrystallizations. Ultimately, the less soluble dibenzoyl tartrate and *p*-bromotartranilate salts[23] were employed to effect the desired resolution. Three to four recrystallizations of these salts furnished the completely resolved amine **6b** in 68 and 71% yields, respectively. The enantiomeric excess was shown to be greater than 97% as determined by ^{1}H NMR of the urea derivative.

Conversion of the resolved amine to optically active aminohexoses with the *lyxo* and *xylo* configurations followed the procedure previously establihsed for the racemic compounds. Benzoylation of **6b** provided the benzamide **6c** that upon hydroxylation furnished the lactones **7a** ($[\alpha]^{23}_D$ −16°) and **8a** ($[\alpha]^{23}_D$ −76°). Acetylation followed by reduction (DIBAL, THF) and ammonolysis afforded L$_s$-*N*-benzoyldaunosamine (**1b**) ($[\alpha]^{26}_D$ −106.2°) in 51% yield and the D-*xylo* isomer **11** ($[\alpha]^{22}_D$ +84°) in 68% yield.

The optical rotation of L$_s$-**1b** was identical in both sign and magnitude with the literature value.[2] The TLC, ^{1}H NMR, IR, and mixed melting point were indistinguishable from those of an authentic sample generously provided by Dr. S. Penco of Farmitalia, S.A., Milan, Italy.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 spectrophotometer and are expressed in reciprocal centimeters. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a JEOL FX90Q spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a CEC Du Pont Model 21-110B or a Du Pont Model 21-491B spectrometer at an ionizing voltage of 70 eV. Optical rotatons were obtained by using a Zeiss polarimeter. Carbon and hydrogen analyses were performed by Galbraith Laboratories.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. with 5% ethyl acetate–dichloromethane as the eluent. Preparative TLC chromatography was performed on 20 × 20 cm precoated silica gel GF plates (layer thickness 0.25 cm) manufactured by Analtech, Inc. Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH). Solvents were reagent grade and were not usually purified prior to use. Hydroxylations were performed with a stock solution of osmium tetraoxide (1 g of OsO_4 in 200 mL of 3:1 *t*-BuOH–CCl_4).

Chlorosulfonyl isocyanate, D-tartaric acid, (−)-dibenzoyl-L-tartaric acid, and (*R*)-(+)-α-methylbenzyl isocyanate were purchased from Aldrich Chemical Co. (*E*)-1,3-Pentadiene was purchased from Chemical Samples Co.

4-((*E*)-Propenyl)-2-azetidinone (5).[8] Chlorosulfonyl isocyanate (**4**) (51 g, 0.37 mol) was added dropwise to a stirred solution of (*E*)-1,3-pentadiene (**3**) (25 g, 0.37 mol) in ether at −10 °C. Upon complete addition, the solution was allowed to warm to 0–5 °C and stirred 1 h at this temperature. The resulting yellow-orange solution was cooled to −78 °C, transferred to an addition funnel wrapped with a towel containing dry ice, and added dropwise to a mixture of aqueous sodium sulfite (25%, 220 mL) and ether (100 mL) at 0–5 °C. This reaction was exothermic, and it was essential to maintain this temperature (0–5 °C) within the reaction flask; otherwise the yield was modest. The aqueous layer was carefully maintained at pH 7–9 by addition of 15% potassium hydroxide. After complete addition, the reaction mixture was stirred at room temperature for 0.5 h. The layers were then separated, and the aqueous portion was extracted with ether (4 × 250 mL). The combined organic solution was dried (Na_2SO_4) and the solvent removed at reduced pressure by using a water bath (no heat) to furnish a pale yellow oil. Purification of the crude product by vacuum distillation (75 °C/0.2 mm) gave 29 g (71%) of pure **5** as a colorless oil: ^{1}H NMR δ 6.24 (b s, 1 H), 5.20–5.92 (m, 2 H), 4.04 (m, 1 H), 3.17 (dd, J = 14.84 Hz, J = 5.06 Hz, J = 1.98 Hz, 1 H), 2.65 (dd, J = 14.84 Hz, J = 2.64 Hz, J = 1.54 Hz, 1 H), 1.71 (d, J = 5.27 Hz, 3 H).

Methyl (±)-3-Amino-4(*E*)-hexenoate Hydrochloride (6a). Dry hydrogen chloride was injected for 1 min into a cold (0–5 °C), magnetically stirred solution of the propenylazetidinone **5** (21.3 g, 0.192 mol) dissolved in dry methanol (250 mL). The reaction was allowed to come to room temperature and after 1.5 h was evaporated at reduced pressure. The residue was recrystallized from acetone–hexanes to furnish 27 g (100%) of the amine hydrochloride **6a** as colorless needles: mp 117–120 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (b s, 1 H), 5.40–6.18 (m, 2 H), 4.18 (m, 1 H), 3.73 (s, 3 H), 2.90 (t, 2 H), 1.74 (d, J = 5.28 Hz, 3 H).

Methyl (±)-3-Benzamido-4(*E*)-hexenoate (6c). To a magnetically stirred solution of the amine hydrochloride **6a** (18 g, 0.10 mol) in water (100 mL) was added a saturated solution of sodium carbonate (24 g, 0.20 mol) in water. The mixture was transferred to a separatory funnel, and the aqueous phase was repreatedly extracted with ether (4 × 100 mL). The combined ether extracts were washed with brine, then dried (Na_2CO_3), filtered, and evaporated at reduced pressure to give 11.6 g (81%) of the free amine **6b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.35–5.90 (m, 2 H), 5.24 (b s, 2 H), 3.70 (m, 1 H), 3.64 (s, 3 H), 2.2–2.6 (m, 2 H), 1.63 (d, J = 5.28 Hz, 3 H).

To a magnetically stirred cold (0 °C) solution of the amine **6b** (11.6 g, 81 mmol) in ether (200 mL) containing pyridine (20 mL) was added benzoyl chloride (12.7 g 90 mmol) in ether (50 mL). When the addition was finshed, the reaction was stirred at room temperature for 1 h. Water (200 mL) was slowly added to dissolve the solids and destroy the excess benzoyl chloride. The reaction was transferred to a separatory funnel and the layers separated. The aqueous phase was further extracted with ether (2 × 200 mL),

(20) The only identifiable products were sorbate derivatives from elimination of the benzamide group.
(21) Kugawa, K.; Yamada, S. *Tetrahedron Lett.* **1969**, 699.
(22) The 3-benzamido acid **6d** was prepared by base (NaOH, H_2O, EtOH) hydrolysis of **6c**.
(23) Montzka, T.; Pindell, T. L.; Matiskella, J. D. *J. Org. Chem.* **1968**, *33*, 3993.

and the combined ether extracts were successively washed with aqueous hydrochloric acid (10%), water (2 × 100 mL), and brine (100 mL). The ether solution was dried ($MgSO_4$), filtered, and evaporated. The residue was recrystallized to give 16.02 g (80%) of the benzamide **6c** as colorless needles: mp 74–76 °C; ^1H NMR ($CDCl_3$) δ 7.70–7.90 (m, 2 H), 7.32–7.58 (m, 3 H), 7.08 (b d, 2 H), 5.38–5.98 (m, 2 H), 4.80–5.18 (m, 1 H), 3.71 (s, 3 H), 2.73 (d, J = 5.06 Hz, 2 H), 1.69 (dd, J = 4.83 Hz, J = 1.1 Hz, 3 H).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.99. Found: C, 68.08; H, 7.05.

DL-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone (7a) and DL-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone (8a). A mixture of the amide **6c** (4.0 g, 16 mmol), trimethylamine N-oxide (4.50 g, 40.4 mmol), and osmium tetraoxide (1.0 mL of stock solution) in acetone (36 mL) and water (1.5 mL) was stirred at room temperature overnight. Analysis of a TLC showed complete consumption of the amide **6c** and the presence of two polar components. A saturated solution of sodium bisulfite (10 mL) was added to the reaction that immediately gave a black precipitate of osmium dioxide. The reaction was transferred to a separatory funnel, and the aqueous phase was extracted with ethyl acetate (4 × 200 mL). The combined ethyl acetate extracts were washed with brine (100 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed on silica (100 g, 3% MeOH–CH_2Cl_2) to give 1.40 g (35%) of the *xylo* lactone **8a** followed by 2.52 g (63%) of the *lyxo* lactone **7a**. Recrystallization of **8a** from acetone–hexanes gave colorless needles: mp 155–156 °C; IR 1787 cm^{-1}; ^1H NMR (acetone-d_6–D_2O) δ 7.86–7.97 (m, 2 H), 7.33–7.65 (m, 3 H), 5.11 (q, J = 8.13 Hz, 1 H), 4.64 (dd, J = 7.25 Hz, J = 2.75 Hz, 1 H), 2.95 (dd, J = 17.47 Hz, J = 8.55 Hz, 1 H), 2.72 (dd, J = 17.47 Hz, J = 7.47 Hz, 1 H), 1.29 (d, J = 6.37 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 62.70; H, 6.12.

Recrystallization of the *lyxo* lactone **7a** from ethyl acetate–hexanes gave colorless needles: mp 136–138 °C; IR 1779 cm^{-1}; ^1H NMR (acetone-d_6/D_2O) δ 7.94–8.00 (m, 2 H), 4.82 (m, 1 H), 4.42 (dd, J = 4.42 Hz, J = 3.52 Hz, 1 H), 4.09 (dd, J = 6.59 Hz, J = 2.64 Hz, 1 H), 3.09 (dd, J = 18.01 Hz, J = 8.78 Hz, 1 H), 2.65 (dd, J = 18.01 Hz, J = 4.62 Hz, 1 H), 1.27 (d, J = 6.37 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 62.60; H, 6.01.

DL-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone Acetate (8b). Acetylation of the *xylo* lactone **8a** (1.28 g) with acetic anhydride (25 mL) and pyridine (5 mL) gave, after workup and recrystallization (acetone–hexanes), 1.35 g (90%) of the acetate **8b** as colorless needles: mp 158–159 °C; ^1H NMR ($CDCl_3$) δ 7.70–7.90 (m, 2 H), 7.40–7.60 (m, 3 H), 7.02 (b d, 1 H), 5.04–5.48 (m, 2 H), 4.64 (dd, J = 7.04 Hz, J = 3.74 Hz, 1 H), 2.95 (dd, J = 17.69 Hz, J = 9.01 Hz, 1 H), 2.43 (dd, J = 17.69 Hz, J = 7.91 Hz, 1 H), 2.08 (s, 3 H), 1.36 (d, J = 6.37 Hz, 3 H).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88. Found: C, 61.91; H, 5.95.

DL-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone Acetate (7b). A procedure identical with that employed to prepare **8b** was used to prepare **7b**. From **7a** (1.0 g) there was obtained 1.0 g (86%) of **7b** after recrystallization (acetone–hexanes): mp 158–159 °C; ^1H NMR ($CDCl_3$) δ 7.70–7.90 (m, 2 H), 7.40–7.60 (m, 3 H), 7.02 (b d, 1 H), 5.07–5.38 (m, 1 H), 4.56–4.80 (m, 1 H), 4.51 (t, J = 3.08 Hz, 1 H), 3.06 (dd, J = 18.24 Hz, J = 8.35 Hz, 1 H), 2.60 (dd, J = 18.24 Hz, J = 3.51 Hz, 1 H), 2.06 (s, 3 H), 1.37 (d, J = 6.59 Hz, 3 H).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88. Found: C, 61.87; H, 5.91.

DL-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyfuranohexose 5-Acetate (9). A solution of diisobutylaluminum hydride (DIBAL) (3.05 mL) in THF (7 mL) was prepared in an addition funnel and then rapidly added to a magnetically stirred, cold (−100 °C; ether–dry ice) solution of the *lyxo* lactone acetate **8b** (300 mg, 1.03 mmol) in THF (20 mL). The reaction was maintained at −100 °C for 3 h and then quenched with methanol–water (5 mL, 4:1). The mixture was allowed to warm to room temperature, and sodium potassium tartrate solution (20 mL, saturated) was added. The reaction was transferred to a separatory funnel and extracted with ethyl acetate (4 × 50 mL). The combined ethyl acetate extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography (silica gel, 10 g, 3–10% MeOH–CH_2Cl_2) of the residue gave, after recrystallization (acetone–hexanes), 227 mg (75%) of **9** as colorless needles: mp 161–162 °C; ^1H NMR ($CDCl_3$–D_2O) δ 7.70–7.90 (m, 2 H), 7.36–7.68 (m, 3 H), 5.68 (d, J = 4.4 Hz, 1 H), 4.84–5.40 (m, 1 H), 4.40–4.70 (m, 1 H), 4.10–4.30 (m, 1 H), 1.8–2.56 (m, 2 H), 2.08 (s, 3 H), 1.34 (d, J = 6.59 Hz, 3 H).

DL-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyhexose (1b). Ammonia was injected for 5 min into a stirred, cold (0 °C) solution of the acetoxy lactol **9** (187 mg, 0.64 mmol) in methanol. The reaction was continued for 2 h at room temperature at which time analysis of a TLC showed complete disappearance of the starting material. The solvent was removed at reduced pressure, and the residue was recrystallized from acetone–hexanes to give 160 mg (~100%) of pure DL-N-benzoyldaunosamine (**1b**) as colorless plates, mp 165–167 °C. The ^1H NMR and TLC were identical with those of an authentic sample of L_s-N-benzoyldaunosamine (L_s-**1b**).

DL-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyfuranohexose 5-Acetate (10). Reduction of the *xylo* lactone acetate **8b** was performed in a manner analogous to that employed to prepare **9**. From **8b** (250 mg, 0.86 mmol) there was obtained 145 mg (58%) of **10**: ^1H NMR ($CDCl_3$, D_2O) 7.68–7.90 (m, 2 H), 7.30–7.64 (m, 3 H), 5.63 (d, J = 4.4 Hz, 1 H), 4.90–5.54 (m, 2 H), 3.96–4.12 (m, 1 H), 1.80–2.20 (m, 2 H), 1.24 (d, J = 6.15 Hz, 3 H).

L-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexose (11). The ammonolysis procedure employed to prepare **1b** was utilized to furnish **11**. From **10** (100 mg, 0.34 mmol) there was obtained after recrystallization (MeOH–ethyl acetate–hexanes) 85 mg (~100%) of **11**, mp 202–204 °C. The ^1H NMR was identical with those previously reported.

***N*-[3-(1-Methoxy-1-oxo-(*S*)-4(*E*)-hexenyl)]-*N'*-[(*R*)-methylbenzyl]urea ((*SR*)-13) and *N*-[3-(1-Methoxy-1-oxo-(*R*)-4(*E*)-hexenyl)]-*N'*-[(*R*)-methylbenzyl]urea ((*RR*)-13).** A mixture of the racemic amine hydrochloride **6a** (4.85 g, 27.2 mmol), (*R*)-(+)-α-methylbenzyl isocyanate (**12**) (4.0 g, 27.2 mmol), and pyridine (2.15 g) in benzene (50 mL) was stirred and heated at reflux overnight at which time analysis of a TLC showed that the starting amine had been consumed. Water (10 mL) was added to the reaction and the mixture stirred for 1 h at ambient temperature. The reaction was transferred to a separatory funnel, and water (50 mL) and ethyl acetate (100 mL) were added. The aqueous phase was separated and further extracted with ethyl acetate (2 × 100 mL).

The combined organic phases were successively washed with dilute hydrochloric acid (10%, 2 × 50 mL), water (100 mL), and brine (100 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a viscous oil. The residue was taken up in 10% ethyl acetate–methylene chloride and passed through a short column of silica gel (25 g) to give a 1:1 mixture of the diastereoisomers in 80% yield. The ^1H NMR spectrum showed the presence of both isomers. The mixture was recrystallized (acetone–hexanes) to give a single diastereoisomer ((*SR*)-**13**) (56% efficiency): mp 111–112 °C; ^1H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 5.20–5.68 (m, 2 H), 4.30–4.98 (m, 4 H), 3.58 (s, 3 H), 2.49 (d, J = 5.27 Hz, 2 H), 1.63 (d, J = 5.71 Hz, 3 H), 1.44 (d, J = 6.59 Hz, 3 H).

The other diastereoisomer (*RR*)-**13** was obtained with 48% efficiency by recrystallization (ethyl acetate–hexanes) of the filtrate: mp 108–109 °C; ^1H NMR ($CDCl_3$) δ 7.26 (s, 5 H), 5.12–5.68 (m, 2 H), 4.40–5.00 (m, 4 H), 3.61 (s, 3 H), 2.52 (d, J = 5.49 Hz, 2 H), 1.57 (d, J = 5.71 Hz, 3 H), 1.44 (d, J = 6.37 Hz, 3 H).

Resolution of 6b with *p*-Bromotartranilic Acid. To a solution of the free amine **6b** (20.43 g, 0.143 mol) in methanol (50 mL) was added a solution of *p*-bromotartranilic acid[18] (23 g, 72 mmol), prepared from D-tartaric acid, in methanol (50 mL). Since the mixture did not crystallize, the methanol was removed at reduced pressure. The residue was dissolved in hot ethyl acetate (150 mL) to effect crystallization. Subsequent recrystallizations were interrupted before complete crystallization occurred—the different types of crystals can be readily distinguished. Three further recrystallizations from ethyl acetate gave 23.7 g (71%) of the pure tartranilate salt as colorless crystals: mp 111–113.5 °C; $[\alpha]^{24}_D$ +54.33° (*c* 10, H_2O).

The enantiomeric excess was >97% as measured by ^{1}H NMR of the urea derivative (mp 111–112 °C) formed from (*R*)-(+)-α-methylbenzyl isocyanate. This material was authenticated with the pure urea diastereoisomer originally isolated from the racemic amine.

Resolution of (±)-6b with (−)-Dibenzoyl-L-tartaric Acid. To the free amine **6b** (27.53 g, 0.193 mol) dissolved in methanol (60 mL) was added a solution of (−)-dibenzoyl-L-tartaric acid monohydrate (36.31 g, 0.096 mol) and methanol (50 mL). A colorless precipitate formed immediately. The mixture was stirred for 20 min, and the solid was collected by filtration. After four recrystallizations from methanol, 33.9 g (68%) of the pure dibenzoyl tartrate salt was obtained as colorless needles, mp 196–198 °C. The ^{1}H NMR spectrum of the urea derivative, formed from (*R*)-(+)-α-methylbenzyl isocyanate and the free amine from the dibenzoyltartrate salt, was used to determine the enantiomeric excess which was >97%.

Methyl (+)-3-(Benzoylamino)-4(*E*)-hexenoate [(+)-6c]. The amine was liberated from the salt with sodium carbonate and then reacted with benzoyl chloride and pyridine to give the *N*-benzoyl derivative **6c**. Crystallization from benzene–hexanes gave 3.21 g (83%) of pure **6c**: mp 89 °C; $[\alpha]^{23}_D$ +5.4° (*c* 10, methanol).

(+)-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone (7a) and (−)-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone (8a). The optically active olefinic benzoate was hydroxylated in a manner analogous to that employed for the racemic compound. From **6c** (3.10 g, 12.5 mmol) there was obtained 1.70 g (55%) of the optically active *lyxo* lactone **7a** and 1.14 g (37%) of the optically active *xylo* lactone **8a**. Recrystallization (ethyl acetate–hexanes) gave colorless needles of *lyxo*-**7a**: mp 147 °C; $[\alpha]^{23}_D$ −16° (c 1, methanol). Recrystallization (ethyl acetate–hexanes) of *xylo*-**8a** gave colorless crystals: mp 170–173 °C; $[\alpha]^{23}_D$ −76° (*c* 1, methanol).

(+)-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone 5-Acetate (7b) and (−)-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexanoic Acid γ-Lactone 5-Acetate (8b). The individual optically active lactones **7a** and **8a** were acetylated as previously described for the racemic compounds. Acetylation of the *lyxo* lactone **7a** (1.29 g, 5.18 mmol) furnished 1.39 g (92%) of pure **7b**: mp 127–129 °C; $[\alpha]^{26}_D$ −8° (*c* 1, methanol). Acetylation of the *xylo* lactone **8a** (850 mg, 3.39 mmol) gave 0.94 g (95%) of pure **8b**: mp 160–162 °C; $[\alpha]^{26}_D$ −118° (*c* 1, methanol).

(+)-*lyxo*-3-(Benzoylamino)-2,3,6-trideoxyfuranohexose 5-Acetate (9). The chiral acetoxy lactone **7b** (1.25 g, 4.26 mmol) was reduced with DIBAL (12.78 mmol) in THF at −100 °C (ether–dry ice) as described for the racemic compound. Workup and chromatography (silica gel, 20 g, 2–4% MeOH–CH_2Cl_2) gave 730 mg (57%) of the acetoxy lactone **9**. Recrystallization from benzene–petroleum ether (30–65) gave colorless needles of **9**: mp 173–176 °C; $[\alpha]^{22}_D$ +30° (*c* 1, methanol).

L_s-(−)-*N*-Benzoyldaunosamine (L_s-1b). Ammonolysis of the lactol acetate **9** (320 mg, 1.09 mmol) in methanol at 0 °C for 2 h gave, after workup and recrystallization (acetone–hexanes), 244 mg (90%) of pure **1b** as colorless crystals: mp 151.5–153 °C (lit.[2] mp 154–156 °C; $[\alpha]^{26}_D$ −106° (ethanol) (lit.[2] $[\alpha]^{26}_D$ −107.5° (ethanol)). The TLC behavior and ^{1}H NMR spectrum were identical with those of an authentic sample. A mixture melting point determination was undepressed.

(−)-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyfuranohexose 5-Acetate (10). Reduction of the *xylo* acetoxy lactone **8b** (680 mg, 231 mmol) was analogously performed to give 596 mg (78%) of **10**. A sample recrystallized from benzene–hexanes had the following properties: mp 168–170 °C; $[\alpha]^{26}_D$ −30° (*c* 1, methanol).

(+)-*xylo*-3-(Benzoylamino)-2,3,6-trideoxyhexanopyranose (11). Ammonolysis of the acetoxy lactone **10** (80 mg, 0.27 mmol) gave 60 mg (87%) of the benzamido hexose **11**. The recrystallized material (acetone–methanol–hexanes) had the following properties: mp 217–220 °C; $[\alpha]^{22}_D$ +84° (*c* 0.1, methanol).

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Registry No. DL-**1b**, 75812-93-0; L-**1b**, 51996-44-2; **3**, 2004-70-8; **4**, 1189-71-5; (±)-**5**, 75812-84-9; (±)-**6a**, 75812-85-0; (±)-**6b**, 89889-13-4; (*S*)-**6b**·(−)-dibenzoyl-L-tartrate, 89921-33-5; (±)-**6c**, 89921-31-3; (+)-**6c**, 75812-86-1; DL-**7a**, 75812-87-2; L-**7a**, 82266-95-3; DL-**7b**, 75812-88-3; L-**7b**, 89889-15-6; DL-**8a**, 75812-90-7; DL-**8b**, 75812-91-8; D-**8b**, 89889-16-7; DL-**9**, 75812-89-4; L-**9**, 89889-17-8; DL-**10**, 75812-92-9; D-**10**, 89889-18-9; DL-**11**, 75812-94-1; D-**11**, 89889-19-0; (*R*)-**12**, 33375-06-3; (*SR*)-**13**, 89889-14-5; (*RR*)-**13**, 89908-11-2; D-**18a**, 75712-55-9; *p*-bromotartranilic acid, 17447-36-8; (−)-dibenzoyl-L-tartaric acid, 2743-38-6.

Intramolecular Diels–Alder Reactions of 1,2-Diazines: General Indoline Synthesis. Studies on the Preparation of the Central and Right-Hand Segments of CC-1065

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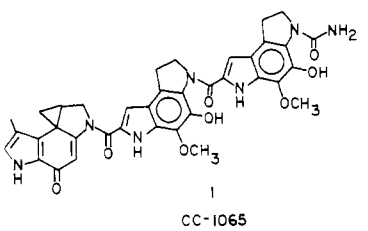
An investigation of the intramolecular Diels–Alder reaction of 1,2-diazines and the application of this cycloaddition to a general synthesis of indolines is described. The use of this cycloaddition in a short, regiospecific preparation of the 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole skeleton, the structural subunit characteristic of the antitumor antibiotic CC-1065, is detailed.

CC-1065, an antitumor antibiotic[2-4] isolated from *Streptomyces zelensis*[3] and identified by X-ray crystallography,[4] is the most potent antitumor agent isolated to date. Preliminary studies indicate that CC-1065 binds



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