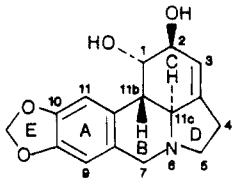
Applications of the Cyclopropyl Iminium Ion Rearrangement. Preparation of Tetracyclic Ring C Functionalized Intermediates Related to Lycorine

Summary: The cyclopropyl iminium ion rearrangement is employed to assemble the spirocyclic ammonium salts **12** from the dihydroisoindole **3** and cyclopropyl aldehyde **9**. The masked dienamine and cinnamate residues, embedded within the spirocyclic ammonium salts **12**, are liberated to provide triene **2**, a substrate suitable for intramolecular [4 + 2] cycloaddition, which upon thermolysis affords the lycorine derivative **13**. Thus, the sequence to **13** provides a highly efficient and convergent entry to derivatives of the lycorine class of Amaryllidaceae alkaloids.

Sir: We have recently described the elaboration of Δ^2-pyrrolinium salts from the corresponding cyclopropyl iminium ions under extremely mild conditions.[1] We now detail an extension of this ring enlargment methodology to the synthesis of a functionalized B,C trans pyrrolo[*d*,*e*]phenanthridine (galanthan) ring system similar to that found in the Amaryllidaceae alkaloid lycorine (**1**). The



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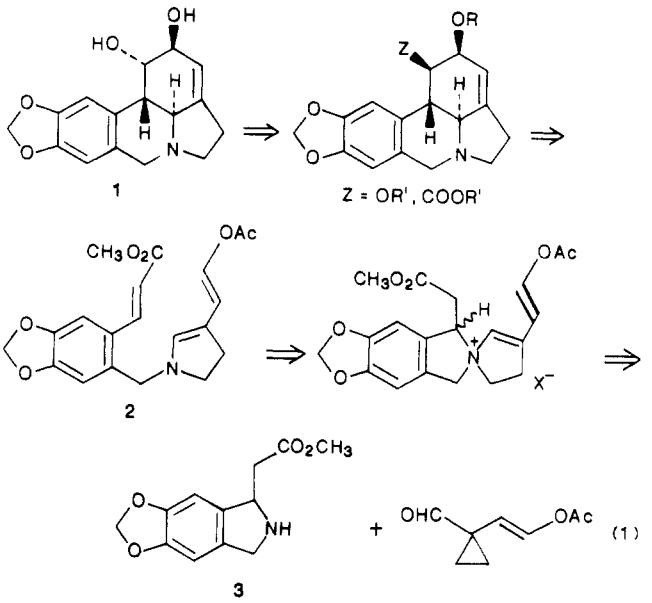
tetracyclic galanthan skeleton has been of considerable interest to organic chemists since the structure of lycorine (**1**) was finally established by Uyeo and Wildman in 1956.[2,3] Indeed, compounds containing this ring system have been found to exhibit significant biological activity as plant growth inhibitors and inhibitors of peptide bond formation in protein synthesis.[4]

Over the years, a number of studies have been undertaken directed toward preparation of the galanthan ring system as well as toward **1** itself.[5] The major synthetic challenge, which was not recognized immediately, derives from the requirement for creation of a trans B,C ring fusion. The required trans arrangement is not the thermodynamically favored B,C ring fusion in the galanthan ring system in spite of the superficial resemblence of rings A, B, and C to a hydrophenanthrene. Unfortunately, the two



synthetic routes which successfully reached lycorine (**1**) developed intermediates in which ring C was underfunctionalized.[6,7] Thus, conversion to **1** required a relatively lengthy series of functional group manipulations which proceed in modest overall yield.[6] We describe below a new approach which allows for the stereospecific construction of the galanthan framework containing a highly functionalized C ring in a simple, concise, and highly convergent manner.[8]

The stereochemical relationships and the position of the unsaturation in ring C of **1** coupled with the requirement to establish the trans B,C ring junction under kinetic control suggested the use of an intramolecular [4 + 2] cycloaddition strategy for construction of the target ring system (eq 1).[8,9] Although it was conceivable, based upon examination of molecular models of a variety of conceivable cycloaddition substrates, that cycloaddition could proceed through either the exo or endo manifold (with respect to the phenyl ring), it appeared that constraining the dienamine unit in a ring would enforce reaction via the required exo transition state.[8] Furthermore, the key cycloaddition substrate, functionalized triene **2**, appeared to be readily accessible by means of our cyclopropyl iminium ion rearrangement methodology (eq 1).[1]

Our sequence to the required dihydroisoindole **3** begins by conversion of (chloromethyl)safrole **4**[10] to protected benzylamine **5** (mp 131–133 °C) by treatment with potassium phthalimide in 93% yield (Scheme I).[11] Degradation of the allyl side chain to benzaldehyde **6** was achieved in 92% overall yield via a two-step procedure involving initial isomerization to the isosafrole derivative **7** (mp 158–159 °C) with $Fe(CO)_5$ (catalytic),[12] and a one-pot, two-stage oxidation of **7** with OsO_4 (catalytic) in the

(1) (a) Boeckman, R. K., Jr.; Jackson, P. F.; Sabatucci, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 2191. (b) Sabatucci, J. P. Ph.D. Dissertation, University of Rochester, 1983.

(2) Extensive chemical and spectroscopic evidence led to the assignment of the structure of lycorine (**1**) as depicted: (a) Humber, L. E.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Taylor, W. I., Thomas, B. R.; Tsuda, Y.; Tsukamoto, K.; Uyeo, S.; Yajima, H.; Yanaihara, N. *J. Chem. Soc.* **1954**, 4622. (b) Takagi, S.; Taylor, W. I.; Uyeo, S.; Yajima, H. *J. Chem. Soc.* **1955**, 4003. (c) Fales, H. M.; Warnhoff, E. M.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 5885.

(3) The absolute configuration of lycorine (**1**) was proposed by Uyeo in 1959: Nakagawa, Y.; Uyeo, S. *J. Chem. Soc.* **1959**, 3736. The structure and absolute configuration of **1** were confirmed by an extensive series of spectroscopic studies and by X-ray crystallographic analysis of a dihydro derivative: (a) Kotera, K.; Hamoda, Y.; Tori, K.; Aono, A.; Kuriyama, K. *Tetrahedron Lett.* **1966**, 2009. (b) Shiro, M.; Sato, T.; Koyama, H. *Chem. Ind. (London)* **1966**, 1229.

(4) (a) Furasawa, E.; Furasawa, S. Morimoto, S.; Cutting, W. *Proc. Soc. Exp. Biol. Med.* **1971**, *136*, 1168. (b) Furusawa, E.; Suzuki, N.; Ramanathan, S.; Furusawa, S.; Cutting, W. *Ibid.* **1972**, *140*, 1034. (c) Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochem. Biophys. Acta* **1976**, *425*, 342.

(5) For a comprehensive suurvey of previous synthetic work directed toward the galanthan ring system, lycorine, and lycorine derivatives, see: Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634.

(6) (a) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1358. (b) Sano, T.; Kashiwaba, N.; Toda, J.; Tsuda, Y.; Irie, H. *Heterocycles* **1980**, *14*, 1097. (c) Moller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand., Ser. B* **1978**, *32*, 98.

(7) Two formal total syntheses of **1** have also been recorded, the latter by a related cycloaddition approach: (a) Umezawa, B.; Hoshino, O. Sowaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475. (b) See ref 5.

(8) While our studies were in progress, Stork and Morgans reported a model study of this cycloaddition approach: Stork, G.; Morgans, D. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7110.

(9) For an excellent discussion of the stereochemical issues inherent in the intramolecular Diels–Alder reaction, see: Ciganek E. *Org. React. N.Y.* **1984**, *32*, 1.

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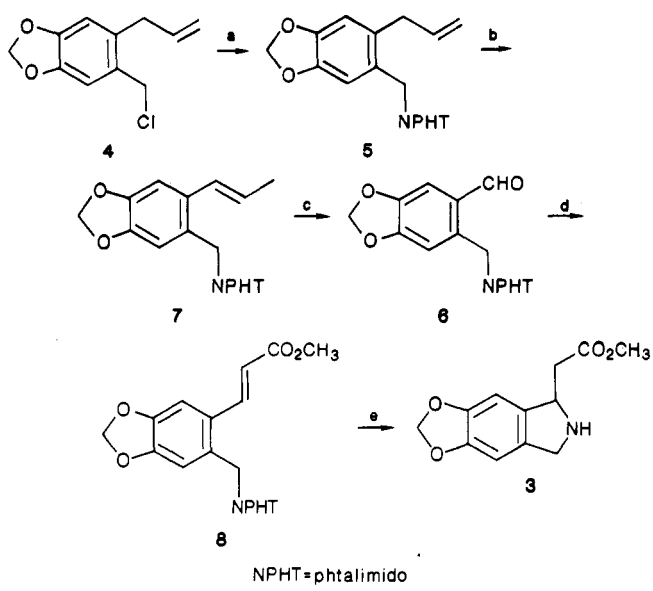
Scheme I[a]



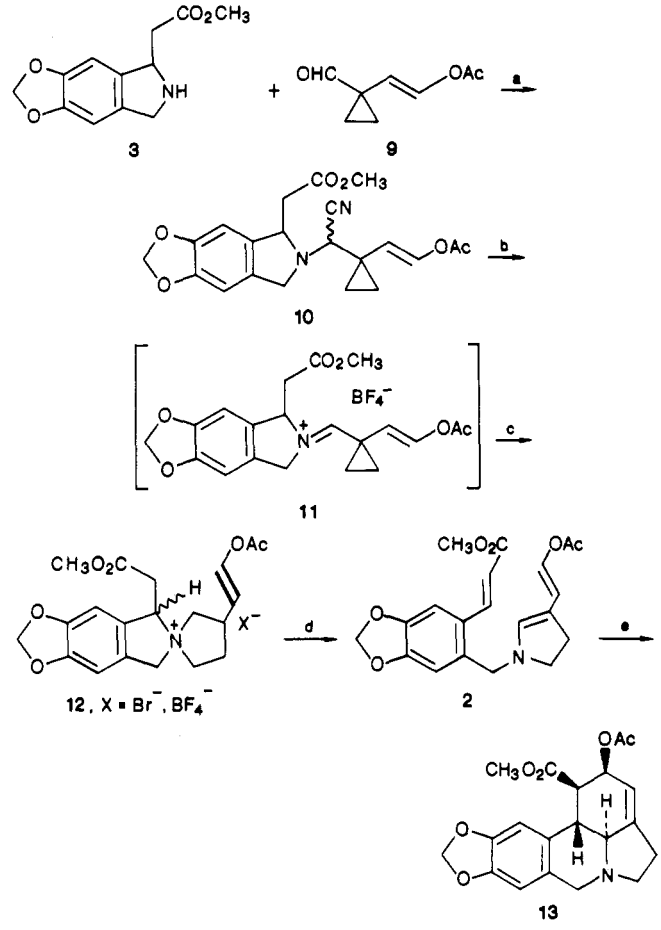
[a] Reagents: (a) K phthalimide (1.16 equiv)/DMF/room temperature/6 h; (b) $Fe(CO)_5$ (0.07 equiv)/xylenes/Δ/1 h; (c) OsO_4 (catalytic)/NMMO (1.15 equiv)/acetone–H_2O (8:5)/0 °C → 25 °C/3 h, then $NaIO_4$ (1.05 equiv)/acetone–H_2O (1:1)/room temperature/1 h; (d) $CH_3O_2CCH_2CO_2H$ (3 equiv)/piperidine (catalytic)/aniline (catalytic)/pyridine/Δ/12 h; (e) NH_2NH_2–n-H_2O (~1.4 equiv)/CH_3OH/Δ/4 h.

presence of *N*-methylmorpholine *N*-oxide (NMMO)[13] and $NaIO_4$.[11] Knovenagel reaction of aldehyde **6** and monomethyl malonate afforded the corresponding cinnamate ester **8** (mp 179–180 °C), which was subjected to hydrazinolysis[14] resulting in cleavage of the phthalimido group and concomitant cyclization of the resulting primary amine via an intramolecular Michael addition providing the oily dihydroisoindole **3** (74% overall from **6**).[11]

The pivotal rearrangement sequence was initiated by condensation of dihydroisoindole **3** (1 equiv), after conversion to the related crystalline perchlorate salt (mp >250 °C), with cyclopropyl aldehyde **9**[1] in the presence of potassium cyanide which afforded the cyano amines **10** (diastereomeric mixture) in up to 76% yield (Scheme II).[11,15] Treatment of this mixture of cyano amines **10** with $AgBF_4$ (1.0 equiv) in DME resulted in immediate precipitation of AgCN and in situ formation of the related cyclopropyl iminium ion **11**.[1] Subsequent addition of anhydrous LiBr (1.0 equiv) effected sequential nucleophilic ring opening of the cyclopropane ring by Br^- followed by intramolecular *N*-alkylation to give the expected diastereomeric spiro Δ^2-pyrrolinium salts **12**. Concentration and precipitation of the salts with ether permitted isolation of the mixture of salts **12** as an amorphous solid in ~52% yield.[11,16]

With the construction of the pyrrolidine ring destined to become ring D of the galanthan skeleton complete,

Scheme II[a]



[a] Reagents: (a) $HClO_4$ (70%) (1.05 equiv till pH 2)/EtOH–CH_2Cl_2/room temperature; then salt was added to **9** (1.53 equiv)/KCN (2 equiv)/$CaCl_2$ (excess)/THF/room temperature/48 h; (b) $AgBF_4$ (1.0 equiv)/anhydrous DME/room temperature/30 min; (c) anhydrous LiBr (1.0 equiv)/anhydrous CH_3CN/room temperature/1 h; (d) DBU (1.24 equiv)/CH_2Cl_2/0 °C/1 h; (e) Δ/$PhCH_3$/4 h.

(10) Pailor, M.; Schleppnick, A. *Monatash Chem.* **1965**, *96*, 1554.

(11) All new substances reported possess spectal data (NMR, IR, MS) consistant with the assigned structure and satisfactory combustion or high resolution mass spectral analytical data. NMR spectral data (400 MHz/$CDCl_3$, unless otherwise indicated): (**2**) δ 7.96 (d, J = 14 Hz, 1 H), 7.15 (s, 1 H), 7.00 (d, J = 12 Hz, 1 H), 6.82 (s, 1 H), 6.20 (d, J = 14 Hz, 1 H), 6.16 (d, J = 12 Hz, 1 H), 6.00 (s, 3 H), 3.94 (s, 2 H), 3.81 (s, 3 H), 3.14 (t, J = 9 Hz, 2 H), 2.54 (t, J = 9 Hz, 2 H), 2.18 (s, 3 H); (**3**) δ (90 MHz) 6.65 (s, 1 H), 6.60 (s, 1 H), 5.91 (s, 2 H), 4.71 (m, 1 H), 4.15 (m, 1 H), 4.15 (s, 2 H), 3.73 (s, 3 H), 2.64 (m, 2 H), 2.44 (s, 1 H); (**5**) δ 10.33 (s, 1 H), 7.85 (m, 2 H), 7.72 (m, 2 H), 7.30 (s, 1 H), 6.83 (s, 1 H), 6.00 (s, 2 H), 5.22 (s, 2 H); (**6**) δ (90 MHz) 7.75 (m, 4 H), 6.85 (s, 1 H), 6.63 (s, 1 H), 5.90 (m, 1 H), 5.85 (s, 2 H), 4.95 (m, 2 H), 4.73 (s, 2 H), 3.55 (m, 2 H); (**8**) δ (90 MHz) 8.35 (d, J = 15 Hz, 1 H), 7.75 (m, 4 H), 7.00 (s, 1 H), 6.91 (s, 1 H), 6.25 (d, J = 15 Hz, 1 H), 5.89 (s, 2 H), 4.90 (s, 2 H), 3.82 (s, 3 H); (**10**) δ 7.20 (d, J = 12 Hz, 1 H), 6.66 (s, 1 H), 6.62 (s, 1 H), 5.95 (s, 2 H), 5.71 (d, J = 12 Hz, 1 H), 4.50 (m, 1 H), 4.45 (s, 1 H), 4.15 (d, J = 11 Hz, 1 H), 3.91 (d, J = 11 Hz, 1 H), 3.72 (s, 3 H), 2.73 (m, 2 H), 2.10 (s, 3 H), 1.08 (m, 2 H), 0.93 (m, 2 H); (**12**) diastereomer 1 δ 7.57 (d, J = 13 Hz, 1 H), 6.82 (s, 1 H), 6.72 (s, 1 H), 6.37 (s, 1 H), 6.20 (d, J = 13 Hz, 1 H), 6.03 (s, 2 H), 5.45 (m, 1 H), 5.07 (d, J = 14 Hz, 1 H), 4.26 (m, 2 H), 3.73 (s, 3 H), 3.12 (m, 1 H), 3.10 (m, 2 H), 2.88 (m, 1 H), 2.20 (s, 3 H); diastereomer 2 δ 7.56 (d, J = 13 Hz, 1 H), 6.81 (s, 1 H), 6.70 (s, 1 H), 6.44 (s, 1 H), 6.15 (d, J = 13 Hz, 1 H), 6.03 (s, 2 H), 5.40 (m, 1 H), 5.07 (d, J = 14 Hz, 1 H), 4.90 (d, J = 14 Hz, 1 H), 4.24 (m, 2 H), 3.76 (s, 3 H), 3.15 (m, 1 H), 3.12 (m, 2 H), 3.07 (m, 1 H), 2.20 (s, 3 H); (**13**) δ 6.64 (s, 1 H), 6.56 (s, 1 H), 5.91 (s, 2 H), 5.77 (s, 1 H), 5.51 (s, 1 H), 3.95 (d, J = 13 Hz, 1 H), 3.78 (s, 3 H), 3.76 (d, J = 13 Hz, 1 H), 3.06 (m, 2 H), 3.03 (m, 1 H), 2.75 (m, 1 H), 2.69 (m, 1 H), 2.62 (m, 2 H), 2.04 (s, 3 H); (**15**) δ (300 MHz) 6.57 (s, 1 H), 6.30 (s, 1 H), 5.89 (s, 2 H), 5.63 (m, 1 H), 5.39 (m, 1 H), 5.15 (dd, J_1 = 6 Hz, J_2 = 6 Hz, 1 H), 4.35 (dd, J_1 = 6 Hz, J_2 = 5 Hz, 1 H), 4.09 (d, J = 14 Hz, 1 H), 3.50 (d(br), J = 14 Hz, 1 H), 3.25 (m, 1 H), 3.09 (dd, J_1 = 10.3 Hz, J_2 = 10 Hz, 1 H), 2.87 (m, 1 H), 2.43 (m, 1 H), 2.27 (d(br), J = 10.3 Hz, 1 H).

(12) De Pasquale, R. J. *Synth. Comm.* **1980**, *10*, 225.

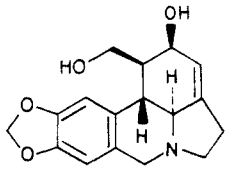
(13) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(14) Sasaki, T.; Minamoto, K.; Itoh, H. *J. Org. Chem.* **1978**, *43*, 2320.

(15) A nonaqueous modification of the Strecker synthesis of α-cyano amines was employed which was based on the method for iminium salt formation described by Leonard: Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021. The yield of cyano amines was occasionally inconsistent ranging from ~50–76% depending upon the run. The factors leading to this variability are not yet understood.

(16) The salts **12** are obtained as a mixture of counterions (Br^- and BF_4^-) as well as being a mixture of diasteromers, thus preventing convenient purification by recrystallization at this stage.

attention was focused on the liberation of the dienophile unit of the Diels–Alder precursor **2**. The amino group has been employed as a means for protection and regeneration of activated olefins for many years.[17,18] This protocol, which has been exploited in our laboratories as well, provided a particularly expedient solution in the present instance since the protection/deprotection operations arise as a natural consequence of the method for assembly of **2** (eq 1).[1] Accordingly, treatment of the dienammonium esters **12** with DBU (1.25 equiv) at 0 °C smoothly afforded the labile triene **2** after rapid filtration chromatography on Florsil. The ^{1}H NMR spectrum (400 MHz) of **2** provided unequivocal evidence for the presence of two *E*-disubstituted olefins (J = 14 Hz, unsaturated ester; J = 12 Hz, enol acetate).[11]



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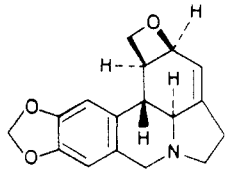

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Due to the sensitivity of triene **2** to both acid and base, the subsequent [4 + 2] cycloaddition was conducted without additional purification by thermolysis of **2** in toluene (25 mg/7 mL) at 110 °C (4 h, ammonia washed glassware, 2 mg of BHT) providing a single tetracyclic ester **13** (mp 174–176 °C) in ~64% yield (from **12**) (Scheme II).[11,19] The complete stereostructure of **13** could not, unfortunately, be assigned on the basis of the ^{1}H NMR (400 MHz) spectrum although the gross structure was confirmed. The magnitude of the crucial coupling constant between H_{11b} and H_{11c} associated with the B, C ring junction stereochemistry could not be resolved. We were able, however, to transform **13** into a compound whose spectral characteristics permitted an unequivocal assignment of the crucial B,C ring junction stereochemistry. To this end, reduction of **13** in THF with excess Dibal in toluene (0 °C) followed by workup using aqueous Rochelle salt afforded diol **14** in good yield (~80%).[11] Selective tosylation of the primary hydroxyl group of **14** (1.2 equiv of TsCl, pyridine, DMAP) and base treatment (KO-*t*-Bu, $(CH_3)_2SO$, room temperature, 30 min) gave oxetane **15** as the sole product.[11] Extensive homonuclear decoupling studies of **15** at 300 MHz established that H_{11b} (δ 3.09) and H_{11c} (δ 2.27) had a common coupling constant of 10.3 Hz, consistant with the assignment of a trans B,C ring junction in **15** and by inference in tetracyclic ester **13** as well.

The extension of this chemistry to the total synthesis of lycorine (**1**) itself, both by appropriate modification of the dienophile unit early in the sequence and by conversion of intermediates such as **13** or **15**, already in hand, to **1**, is currently under investigation.

Acknowledgment. We thank the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health for a research grant (GM-29290) in support of these studies. We also express appreciation for the award of an NSRA fellowship (GM-09624) from the National Institute of General Medical Sciences to S.W.G.

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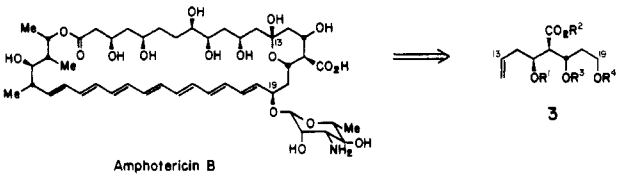
The Asymmetric Synthesis of Branched-Chain Polyketide Compounds through Stereoselective Aldol Condensations of β-Heteroatom Ester Enolates

Summary: The high stereoselectivity of aldol condensations using the enolate derived from β-amino thiol ester **7** forms the basis for an efficient synthetic approach to branched chain polyketide carbon skeletons.

Sir: Polyketide-derived natural products are mostly commonly comprised of linear 1,3-oxygenated arrays of the general type **1**. However, a significant number of compounds within this class, exemplified by amphotericin B,[1] tylosin,[2] and streptovaricin A,[3] incorporate oxygenated arrays (**2**) that are branched in nature. In contrast to the



diversity of elegant synthetic approaches to linear arrays (**1**),[4] relatively few methods have emerged for the asymmetric preparation of branched-chain carbon skeletons of the type **2**.[5] As part of a study targeting the synthesis of amphotericin B, we required an efficient synthesis of the branched chain C13–C19 subunit in the form of **3**.[6] We report herein a study of the stereoselective aldol condensations of enolates derived from β-heteroatom esters and the subsequent application of these results to a concise synthesis of a fragment (**13**) containing the key features of **3**.

(17) (a) Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron* **1976**, *32*, 765. (b) Van Tamelen, E. E.; Bach, S. R. *J. Am. Chem. Soc.* **1955**, *77*, 4683.

(18) For related examples of the use of spirocyclic ammonium salts, see: Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335 and references therein.

(19) The yield of this cycloaddition is sensitive to the presence of impurities in the triene **2** which catalyze polymerization.

(1) (a) Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873. (b) Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560.

(2) Omura, S.; Matsubara, H.; Nakagawa, H. *J. Antibiot.* **1980**, *33*, 915.

(3) Rinehart, K. L., Jr.; Antosz, F. J.; Sasaki, K.; Martin, P. K.; Maheshwari, M. L.; Reusser, F.; Li, L. H.; Moran, D.; Wiley, P. F. *Biochemistry* **1974**, *13*, 861.

(4) For relevant reviews: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3549. (b) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 4. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(5) For recent studies: (a) Boschelli, D.; Ellingboe, J. W.; Masamune, S. *Tetrahedron Lett.* **1984**, *25*, 3395. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(6) For other studies addressing this fragment, see: (a) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (b) See ref 5c.

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