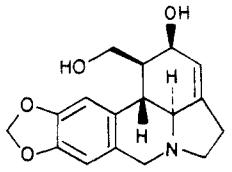
attention was focused on the liberation of the dienophile unit of the Diels–Alder precursor **2**. The amino group has been employed as a means for protection and regeneration of activated olefins for many years.[17,18] This protocol, which has been exploited in our laboratories as well, provided a particularly 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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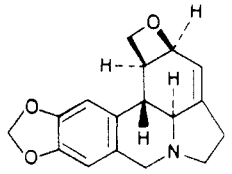

15

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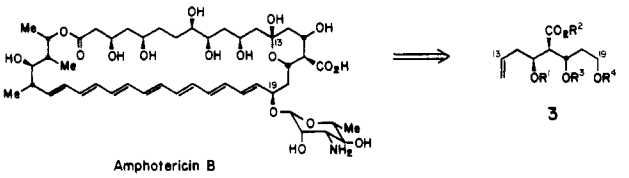
The Asymmetric Synthesis of Branched-Chain Polyketide Compounds through Stereoselective Aldol Condensations of β-Heteroatom Ester Enolates

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.

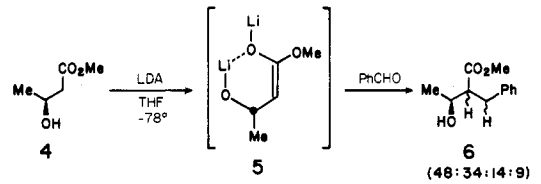
(4) For relevant reviews: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3549. (b) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 4. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, 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.

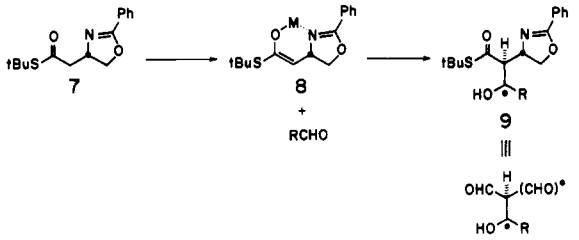
(6) For other studies addressing this fragment, see: (a) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (b) See ref 5c.

0022-3263/86/1951-3742$01.50/0

Scheme I



Scheme II

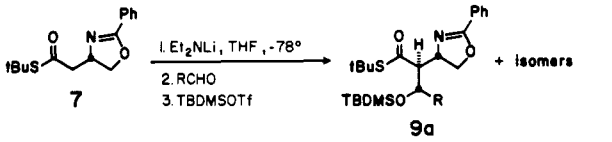


An attractive solution to the problem at hand seemed to lie in the suitable elaboration of a β-hydroxy ester such as **4** (Scheme I). While it has been established that derived enolate dianions **5** participate in highly selective alkylation reactions,[7] the corresponding aldol condensation (with PhCHO) was found to proceed with disappointingly low levels of selectivity (**6** as a 43:34:14:9 mixture[8]). Reasoning that kinetic stereoselection may be adversely affected by the presence two metal centers in **5**, we were hopeful that the simple chelated enolate **8**, derived from chiral β-amino thiol ester **7**[9] (see Scheme II), would find less ambiguity in its transition-state interactions with a carbonyl component. Furthermore, the functional equivalence of the thiol ester and oxazoline moieties (vide infra) in adduct **9** introduces an element of latent symmetry, expanding the stereochemical flexibility of this approach.

By analogy to previous alkylation studies,[9] we anticipated that chelated enolates **8** would exhibit high diastereofacial discrimination in aldol condensations, although the question of facial selection in the aldehyde component remained to be addressed. As the results in Table I indicate, high levels of facial discrimination for *both* components are generally observed. In an effort to improve the condensation with propanal (entry 1), changes in the solvent (Et_2O, DME) and metal ion (MgCl, ZnCl, Et_2B, Cp_2ClZr) invariably led to lower selectivity for isomer **9a**. Of particular note are the exceptional levels of selection observed when an α,β-unsaturated aldehyde is employed (entries 3–8). The bias for isomer **9a** in these cases is somewhat diminished upon introduction of electron-donating groups to the conjugated π-system.

The stereochemical results of this study parallel those observed in aldol condensations using magnesium enolates derived from α-sulfinyl esters.[10] Of the three possible

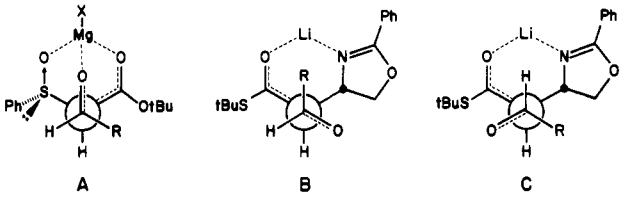
Table I



Entry	RCHO	Yield (%)[a]	9a:(isomers)[b]
1	C_2H_5CHO	70	77:(18:5)
2	$tBuMe_2SiO$ CHO	67	79:(21)
3	PhCHO	89	>50:(1)
4	MeO, MeO, MeO, CHO	99	87:(13)
5	O_2N CHO	92	95:(3:1:1)
6	CHO	95	>50:(1)
7	PhS CHO	>40	84:(13:3)
8	Me_3Si CHO	91	20:(1)

[a] Yield of purified product. [b] Ratios are obtained by the integration of the ^1H NMR. Relative amounts of observable isomers other than **9a** are given in the parentheses.

staggered transition-state models possessing the correct orientation of the reacting π-faces, model A was invoked to explain these previous results.[10] In the present case,



we are inclined to eliminate a transition state such as A on the basis of the strain energy expected to accompany the metal–aldehyde interaction on an array possessing a high degree of planarity.[11] Further consideration of developing gauche interactions and pseudo-1,3-diaxial R ⇄ metal ligand interactions presently biases our judgment in favor of transition-state model C. However, it is clear that further work is needed to illuminate the steric and electronic details of these highly ordered activated complexes.

While the stereocontrolling factors remain obscure in the condensations employing unsaturated aldehydes, the results are of considerable synthetic utility. For example, the adduct derived from condensation of thiol ester **7** with acrolein (**10**) may be efficiently transformed into a potential precursor for the C13–C19 subunit of amphotericin B by the route depicted in Scheme III. Reduction of **10** with Dibal at −78 °C smoothly affords aldehyde **11** which suffers stereospecific allylation with diallylzinc to yield **12** following protection. This stereochemical outcome is presumably dictated by a strong nitrogen–zinc interaction

(7) For alkylations of β-hydroxy esters: (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2829. (c) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. (d) Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383. (e) Zuger, M.; Weller, Th.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. (f) Frater, G. *Tetrahedron Lett.* **1981**, *22*, 425. (g) Wasmuth, D.; Arigoni, D.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 344. (h) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928. (i) Bajwa, J. S.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 1114.

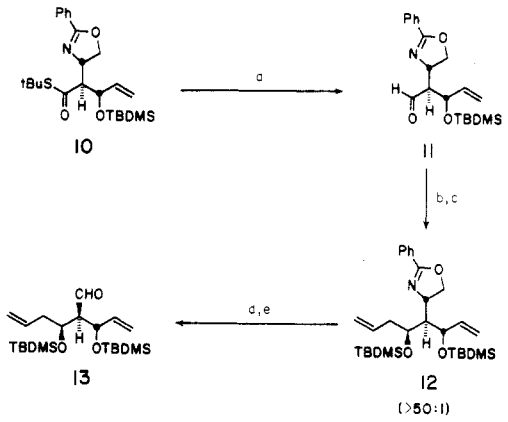
(8) Determined by capillary GLPC analysis on the derived acetonide [$Me_2C(OMe)_2$, TsOH, (cat.)]. The condensation of the species resulting from treatment of **5** with $MgBr_2$ gave a 51:39:5:5 mixture of isomers.

(9) Compound **7** is prepared in optically pure form in seven steps from L-aspartic acid: (a) McGarvey, G. J.; Hiner, R. N.; Matsubara, Y.; Oh, T. *Tetrahedron Lett.* **1983**, *24*, 2733. (b) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.*, in press.

(10) (a) Mioskowski, C.; Solladie, G. *J. Chem. Soc., Chem. Commun.* **1977**, 162. (b) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227.

(11) Bond angles and bond lengths appear to preclude simultaneous bond formation and a metal–aldehyde interaction. Furthermore, it is not clear what factors bias the facial orientation of the aldehyde in A.

Scheme III[a]



[a] (a) Dibal, PhMe, −78 °C; (b) $Zn(allyl)_2$, THF, 0 °C; (c) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) Dibal, PhMe, 0 °C; (e) $NaIO_4$, EtOH, H_2O.

on an intervening chelate. The oxazoline is unmasked through reductive cleavage to a benzylamino alcohol[12] which is subsequently oxidized to aldehyde **13** through exposure to $NaIO_4$. Compound **13**, isolated as a single isomer in greater than 50% overall yield from **7**, may serve as a convenient precursor to subunits bearing side-chain carboxyl (amphotericin B, streptovaricin A) and hydroxy methylene groups (tylosin).

In summary, we have shown that β-amino thiol ester **7** may engage in highly stereoselective aldol condensations to afford adducts that are useful intermediates for branched-chain polyol fragments (e.g., **2**). The latent symmetry of **7** and its readily accessible enantiomer[13] confers considerable stereochemical latitude to this approach. Further application of this strategy to the synthesis of amphotericin B will be reported in due course.

Acknowledgment is made to the National Institutes of Health (AI 188889) for their generous support of this research.

Registry No. **4**, 1487-49-6; **6** (isomer 1), 103959-37-1; **6** (isomer 2), 103959-38-2; **6** (isomer 3), 103959-39-3; **6** (isomer 4), 103959-40-6; **7**, 102614-13-1; **9** (R = t-$BuMe_2SiOCH_2CH_2$), 103959-51-9; **9** (R = Ph), 103959-52-0; **9** (R = 3,4,5-$(MeO)_3C_6H_2$), 103959-53-1; **9** (R = p-$O_2NC_6H_4$), 103959-54-2; **9a** (R = C_2H_5), 103959-41-7; **9a** (R = t-$BuMe_2SiOCH_2CH_2$), 103959-42-8; **9a** (R = Ph), 103959-43-9; **9a** (R = 3,4,5-$(MeO)_3C_6H_2$), 103959-44-0; **9a** (R = p-$O_2NC_6H_4$), 103959-45-1; **9a** (R = CH_2=CH), 103959-46-2; **9a** (R = PhSCH=CH), 103959-47-3; **9a** (R = Me_3SiCH=CH), 103959-48-4; **11**, 103980-76-3; **12**, 103959-49-5; **13**, 103959-50-8; t-$BuMe_2SiOCH_2CH_2CHO$, 89922-82-7; CH_2=CHCHO, 107-02-8; PhSCH=CHCHO, 78998-83-1; Me_3SiCH=CHCHO, 58107-34-9; PhCHO, 100-52-7; C_2H_5CHO, 123-38-6; 3,4,5-$(MeO)_3C_6H_2CHO$, 86-81-7; p-$O_2NC_6H_4CHO$, 555-16-8; $Zn(allyl)_2$, 1802-55-7.

Supplementary Material Available: Physical and spectral data on the compounds in Table I and Scheme III (3 pages). Ordering information is given on any current masthead page.

(12) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4043.
(13) The enantiomer of **7** is prepared from readily available D-aspartic acid.

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Phase-Managed Organic Synthesis. A New Synthesis of Mixed Formic Anhydrides

Summary: Two new mixed formic anhydrides, cinnamic formic anhydride and formic 4-methoxybenzoic anhydride, can be prepared in high yield (~80%) from equimolar mixtures of sodium formate and the appropriate acid chloride with a solid-phase copolymer of pyridine 1-oxide as catalyst, and they exhibit excellent selectivity as formylating agents of alcohols and amines.

Sir: During a continuing investigation of the application of multiple-phase techniques to organic synthesis, we discovered that a solid-phase copolymer of 4-vinylpyridine 1-oxide[1] (P4-VP-NO) is a particularly effective catalyst for the formation of mixed formic anhydrides, eq 1. This

$$\mathrm{RCOCl + HCOO^-Na^+ \xrightarrow[CH_3CH,\ rt]{P4\text{-}VP\text{-}NO} RCOOCOH + NaCl} \quad (1)$$

1: R = PhCH=CH
2: R = 4-MeOPh

method utilizes mixtures equimolar in acid chloride and sodium formate to obtain high isolated yields (~80%) of the corresponding stable mixed anhydride. Anhydrous acetonitrile proved to be a suitable solvent. Catalysis of the reaction is believed to involve acylation of P4-VP-NO to form the 1-acyloxy derivative **3**, which then acylates formate ion to give the mixed formic anhydride as shown in Scheme I.[2-5] Some results obtained with this new synthetic method are summarized in Table I. It is especially noteworthy that the stable mixed formic anhydrides obtained in this manner are excellent formylating agents, Table II.

Formylation of nucleophiles is an important synthetic procedure accomplished by a wide variety of methods. An effective approach available for relatively unreactive substrates (e.g., alcohols, phenols) uses acetic formic anhydride generated in situ from formic acid–acetic anhydride mixtures with catalysis by tertiary amines.[6-8] Formic anhydride itself is highly unstable and may be studied only at temperatures below −40 °C.[9] It decomposes to formic acid and carbon monoxide, eq 2. Several mixed formic anhydrides are known which vary widely in stability.[10-12]

$$\mathrm{RCOOCOH \rightarrow RCOOH + CO} \quad (2)$$

R = H, alkenyl, alkoxy, alkyl, aryl

(1) The solid-phase copolymer of 4-vinylpyridine 1-oxide used as a catalyst in this study, P4-VP-NO, was prepared by oxidizing Reillex 425, available from Reilly Tar & Chemical Corporation, Indianapolis, with 30% hydrogen peroxide in glacial acetic acid (Ochiai, E. *Aromatic Amine Oxides*; Elsevier Publishing Company: Amsterdam, 1974; p 24).
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(6) (a) Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1287. (b) van Es, A.; Stevens, W. *Ibid.* **1965**, *84*, 704. (c) van Es, A.; Stevens, W. *Ibid.* **1965**, *84*, 1247.
(7) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(8) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.
(9) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M.; Sommer, J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 614.
(10) (a) Schijf, R.; Scheeren, J. W.; van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 594. (b) Schijf, R.; Stevens, W. *Ibid.* **1966**, *85*, 627.
(11) Muramatsu, I.; Murakami, M.; Yoneda, Y.; Hagatani, A. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 244.
(12) Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *Recl.: J. R. Neth. Chem. Soc.* **1982**, *101*, 460.

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