Communications

Synthesis of Monocrotaline by Nucleophilic Macrolactonization

Summary: Monocrotaline (2) has been prepared by a sequence involving the coupling of 10 with 6, followed by nucleophilic ring closure. The cyclization step involes mesylate displacement by carboxylate ion, generated in situ via the desilylation of a β-(trimethylsilyl)ethyl ester 3.

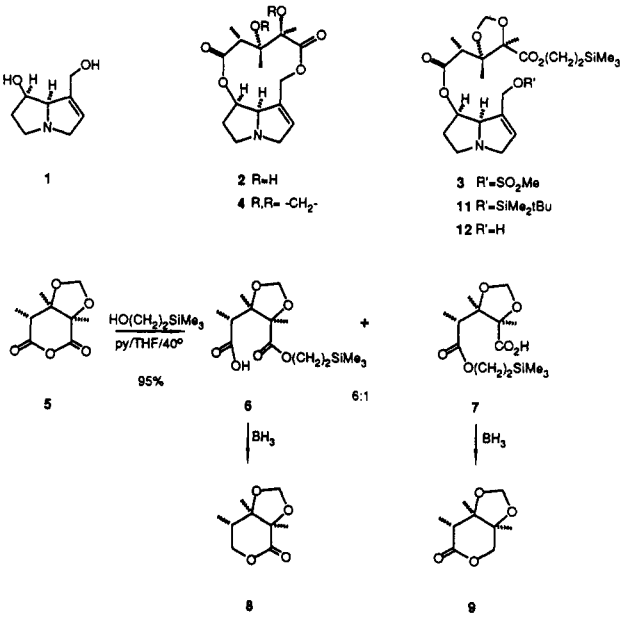
Sir: Macrocyclic dilactone pyrrolizidine alkaloids derived from retronecine (1) are remarkable for their potent hepatotoxic and antitumor activity and for their role as defensive agents and pheremone precursors in Danaid butterflies.[1] Syntheses of some of the simpler dilactones are known,[2] but the important 11-membered derivative monocrotaline (2) poses special problems (Chart I). In particular, its tendency for γ-lactone formation complicates possible synthetic strategies.[3]

Previous work on the fulvine–crispatine series suggested that fluoride-induced cyclization of mesylate 3 to dilactone acetal 4 should be possible.[2a] This procedure is well-suited for complex pyrrolizidine dilactones because it avoids the risks of internal cyclization associated with electrophilic carboxyl activation methods. To confirm that acetal 4 could be deprotected, monocrotaline (2) was converted into 4 (methylal/P_2O_5/$CHCl_3$, room temperature, 98%)[4] and 4 was subjected to acid hydrolysis. Although some degradation proved unavoidable, a 75% yield of monocrotaline could be obtained at 50% conversion by treatment of 4 with 38% HCl + ethylene glycol (110 °C, 2 h). The synthetic problem therefore depends on the preparation of 3 and its conversion into 4.

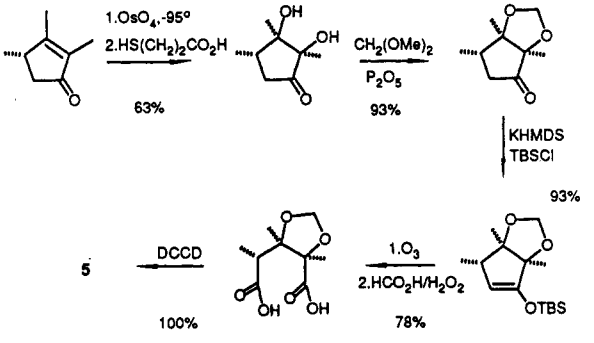
Two routes to 3 have been devised, both of which involve the protected glutaric anhydride derivative 5. In the first route, 4 derived from natural retronecine was saponified (LiOH, 35 °C; quantitative) and the resulting diacid was cyclized to optically pure 5 by using dicyclohexylcarbodiimide (THF, room temperature, quantitative). A second route (Scheme I) involved a series of conventional steps from 2,3,4-trimethylcyclopent-2-enone[5] and produced *d,l*-5. In either case, treatment of 5 with 2-(trimethylsilyl)ethanol (pyridine/THF, 40 °C, 17 h) occurred with interesting selectivity to give 6 and 7 in a 6:1 ratio, 95%. These structures were established by conversion of 6 into 8 ($NaBH_4$ + BF_3, 85%; ^1H NMR, OCH_2CH at δ 4.45, 3.95, J_{AB} = 11.0 Hz, J_{AX} = 3.5 Hz, J_{BX} = 6.0 Hz) and 7 into 9 (86%; ^1H NMR, OCH_2 at δ 4.20, 4.15, J_{AB} = 11.0 Hz).

Selective anhydride cleavage at the more highly substituted carbonyl group has been attributed to the approach trajectory in other systems.[6] However, the dominant factor in the case of 5 is probably the electronic effect of an alkoxy group α to carbonyl. Attack from the exo side (relative to the bicyclic subunit) could thus benefit from the anti alkoxy orientation which is invoked in Felkin–Anh transition states.[7]

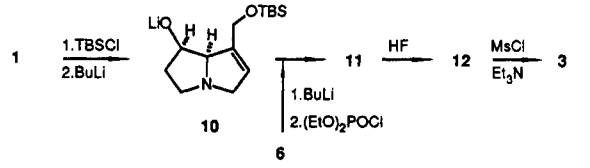
Chart I



Scheme I



Scheme II



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The optically active monoester **6** was coupled in 65% yield by using the mixed phosphoric anhydride method (1 equiv of *n*-BuLi, THF, −78 °C; $(EtO)_2POCl$ to room temperature) with optically pure **10**, obtained from **1** by treatment with *t*-$BuMe_2SiCl$ (TBSCl) followed by *n*-butyllithium (Scheme II). The resulting diester **11** was deprotected with 5% aqueous HF in THF to give **12** (96%). This material was converted into the mesylate **3** ($MsCl/Et_3N/CH_2Cl_2$) and crude **3** was added over 3 h to excess $Bu_4N^+F^-\cdot 3H_2O$ in acetonitrile at 34 °C to effect ring closure to the monocrotaline acetal **4** (71% yield).

The possibility of using *d,l*-**6** in the coupling with **10** was explored briefly. Thus, *d,l*-**6** was converted into the mixed phosphoric anhydride as before and then treated with a deficiency of optically pure **10**. Although a modest 2:1 enantiomer differentiation in favor of the natural isomer **11** was observed, this procedure did not utilize the precursor **6** efficiently. Further experiments with **11** derived from *d,l*-**7** were restricted to demonstrating that this material could be cyclized to the *d,l* dilactone **4** via the desilylation of **3**.

Deprotection of **4** as described earlier affords **2**. Coupled with recent efforts in the synthesis of (±)- or (+)-retronecine,[8] this study completes the total synthesis of monocrotaline. Furthermore, the sequence confirms the generality of the nucleophilic cyclization method for synthesis of retronecine-derived dilactones. As in our earlier report,[2a] the 2-(trimethylsilyl)ethyl ester is converted in situ to a tetrabutylammonium carboxylate under dilution conditions which favor intramolecular displacement of mesylate. Attempts to extend this cyclization method to a relatively simple macrolide have not been promising,[9] but the procedure is remarkably effective in the case of pyrrolizidine alkaloids. There are now four successful examples of cyclization to 11-membered retronecine dilactones,[2a] as well as a recent extension to a 12-membered analogue.[2e]

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Registry No. **2**, 315-22-0; (±)-**2**, 109525-74-8; (±)-**5**, 109391-24-4; (±)-**6**, 109391-25-5; (±)-**7**, 109391-26-6; (±)-**8**, 109391-27-7; (±)-**10**, 89710-47-4; (±)-**11**, 109432-25-9; (±)-**12**, 109391-29-9; (±)-2,3,4-trimethylcyclopent-2-enone, 109391-22-2; (±)-2,3-dihydroxy-2,3,4-trimethylcyclopentanone, 109391-23-3; (±)-3-methylheptane-2,5-dione, 109391-28-8; 3-methylbut-3-en-2-one, 814-78-8; propionaldehyde, 123-38-6; (±)-2,3,4-trimethyl-2,3-dihydroxycyclopentanone methylene acetal silyl enol ether, 109391-30-2; *d,l*-monocrotalic acid methylene acetal, 109494-78-2; (±)-9-*O*-(*tert*-butyldimethylsilyl)retrocene, 89617-46-9; 2-(trimethylsilyl)ethanol, 2916-68-9.

Supplementary Material Available: Experimental details and characterization data for **4–6**, **11**, and **12** (8 pages). Ordering information is given on any current masthead page.

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Kinetic and Product Hydrogen–Deuterium Isotope Effects in Ene Reactions: A Model for Understanding Apparently Anomalous Effects

Summary: Cases in which a concerted and a stepwise ene reaction show an apparently anomalous change in a product hydrogen–deuterium isotope effect with electrophilic activation of the eneophile are reported and shown to be consistent with a kinetic scheme in which a reaction intermediate can partition between the steps of reversal, equilibration of geometrically defined species, and conversion to product.

Sir: Comparisons of kinetic and product hydrogen–deuterium isotope effects have been a powerful tool for making choices between concerted and stepwise mechanisms of a number of formal ene reactions.[1,2] Equal kinetic and product isotope effects in inter- and intramolecular competitions usually are taken as evidence for concert in a single bond-making and bond-breaking step, although Orfanopoulous, Foote, and Smonou recently have made a qualitative suggestion that low isotope effects may be interpreted in terms of partially equilibrating reaction intermediates.[3a] Unequal kinetic and product isotope effects usually are taken to establish the presence of a reaction intermediate.[2-7] In this paper we report apparent anomalies in product isotope effects accompanying activation of the eneophile in both concerted and stepwise mechanisms of the ene reaction. We provide a framework for the interpretation of kinetic and product isotope effects and illustrate how such isotope effects can be quantitatively interpreted in terms of partitioning of a reaction intermediate.

The isotope effects for the thermal and catalyzed ene reactions of methylenecyclohexane (**1**), 2,2-dideuteriomethylenecyclohexane (**1**-d_2), and 2,2,6,6-tetradeuterio-

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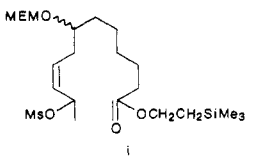
(9) We were unable to isolate a macrolide from attempted cyclization of structure i:[10]



i

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