bromide **3** consumes an additional equivalent of **1** at 25 °C to afford bis(neopentyloxy)triphenylphosphorane (BNTP; 48%; ^{31}P δ −58.3).[6] The ^{13}C (Chart I) and ^{31}P NMR parameters exhibited by BNTP are consistent with the trigonal-bipyramidal conformation with diapical neopentyloxy ligands.[1] The observable couplings, $^{2}J_{POC}$ = 8.8 Hz and $^{3}J_{POCC}$ = 5.0 Hz, are analogous to those observed for $Ph_3P(OEt)_2$ and $Ph_3P(OHex)_2$.[1]

In a typical cyclodehydration reaction (Table I; entry 3), *meso*-1,2-diphenylethane-1,2-diol (642 mg, 3 mmol) was treated with a solution of BNTP (0.5 M, 3 mmol) in dichloromethane solvent (40 °C, 24 h) to afford *trans*-stilbene oxide (>95% by GLC and ^{13}C NMR analyses). The solvent was removed and the sample redissolved in $CDCl_3$: ^{1}H NMR ($CDCl_3$) δ 3.83 (*s*, 2 H, CHOC) and 7.40 (*m*, 10 H, Ar H's); ^{13}C NMR (CH_2Cl_2) δ 62.7 (Ph*C*CPh) with noise decoupling. This result is consistent with the ring closure predictions of Baldwin[12] where the 3-exo-tet cyclization with inversion at the displacement terminus is expected. Tetrahydrofuran and tetrahydropyran are also formed from the respective diols in excellent yields by employing this methodology (Table I, entries 4 and 5).

Previously, we had noted that $Ph_3P(OEt)_2$ mediated conversions of several 1,2-amino alcohols to the corresponding aziridines are excellent if an equivalent of reactant and substrate is maintained. Additional $Ph_3P(OEt)_2$ initiates *N*-ethylation of the aziridinyl nitrogen affording the tertiary amine.[2] However, reaction of 1,2-ethanolamine with 2 equiv of BNTP gives aziridine in >98% with no spectroscopic evidence for N-neopentylation of the parent aziridine. Undoubtedly, the methylene group of $Ph_3P^+OCH_2C(CH_3)_3$ is sufficiently sterically hindered to diminish the effectiveness of aziridinyl nitrogen Arbuzov attack.[2]

Finally, S-ethylation is particularly problematic in the synthesis of cyclic sulfides from reactions of mercapto alcohols with $Ph_3P(OEt)_2$. For example, the cyclodehydration of 4-mercaptobutanol with $Ph_3P(OEt)_2$ gives tetrahydrothiophene (65%) and 4-(ethylthio)butanol (35%).[3] However, BNTP cyclodehydrates 4-mercaptobutanol to tetrahydrothiophene in >98% by ^{13}C NMR and GLC analyses. Competitive thiolate attack on the α methylene carbon is apparently suppressed when the neopentyl group constitutes part of the oxo ligand.

Acknowledgment is made to the Rohm and Haas Company for sponsoring the Americal Chemical Society–Division of Organic Chemistry Fellowship to J.W.K. We are also grateful to the Department of Energy for partial support of this research and to Professor Albert Eschenmoser for his valuable suggestions.

(8) The composition of this material is largely BNTP, lithium bromide,and triphenylphosphine oxide.
(9) Nitrogen gas would be an acceptable substitute.
(10) Reagent-grade hexanes are distilled from calcium hydride under argon.
(11) The ^{31}P chemical shift assigned to **3** (δ 61.7) is similar to that (δ 62) reported for ethoxytriphenylphopshonium tetrafluoroborate [Ph_3P^+OEt,BF_4^-]. See: Denney, D. B.; Denney, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85–89. The ^{13}C shifts of the neopentoxy ligand and the ^{13}C–^{31}P coupling constants are also indicative of the alkoxyphosphonium structure.
(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

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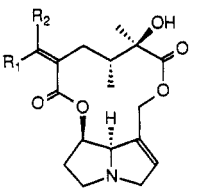
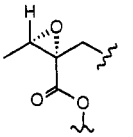
Synthesis of the Macrolactone Pyrrolizidine Alkaloid Integerrimine

Summary: Synthesis of the natural enantiomer of the 12-membered dilactone integerrimine was accomplished by coupling retronecine with a masked version of integerrinecic acid. The latter was acquired in homochiral form from (*R*)-(−)-3-hydroxy-2-methylpropionate.

Sir: The powerful hepatotoxic, carcinogenic, and other physiological properties associated with alkaloids of the pyrrolizidine family have brought these substances to high prominence in recent years.[1] Conspicuous among this group of structures is a set of 12-membered dilactones that includes integerrimine (**1**), its geometrical isomer seneci-



1, R_1 = H, R_2 = CH_3
2, R_1 = CH_3, R_2 = H



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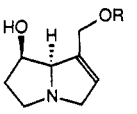

4, R = H
23, R = SitBuMe$_2$

onine (**2**), and the epoxide jacobine (**3**), each of which consists of a dicarboxylic (necic) acid spanning the C-7,C-9 hydroxy functions of retronecine (**4**). Although numerous routes to **4** have been published,[2] less success has attended synthetic efforts directed at the complex macrolactones. However, a recent synthesis of (±)-**1**[3] provides encouraging precedent for a plan that connects the fully functionalized necic acid to its pyrrolizidine base,[4] and we now describe a stereocontrolled synthesis of the natural enantiomer of **1** that assembles the macrolactone from a protected homochiral form of integerrinecic acid and naturally derived (+)-**4**.

The [(trimethylsilyl)ethoxy]methyl (SEM)[5] ether **6** of methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (**5**) was converted to aldehyde **8** via alcohol **7**.[6] Treatment of **8** with methylmagnesium bromide, followed by Swern oxidation,[6] afforded **9** which, in a chelation-controlled Grignard reaction[7] with vinylmagnesium bromide, yielded a 4:1 mixture of the desired alcohol **10** and its diastereomer **11**. These were easily separated (HPLC, μ-Porasil) as their cyclic carbonates, prepared from the mixture of diols with carbonyldiimidazole, and the major carbonate **12**, after hydrolysis to **13**, was transformed to iodo acetate **15** via the primary tosylate **14**.

(1) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115.
(2) Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247. For recent accomplishments in this area, see: Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993. Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *Heterocycles* **1982**, *19*, 2075. Niwa, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125.
(3) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Morimoto, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 455. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guédin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.
(4) Syntheses of (±)-crispatine and (±)-fulvine also employed this strategy (Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030).
(5) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(6) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(7) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1035.

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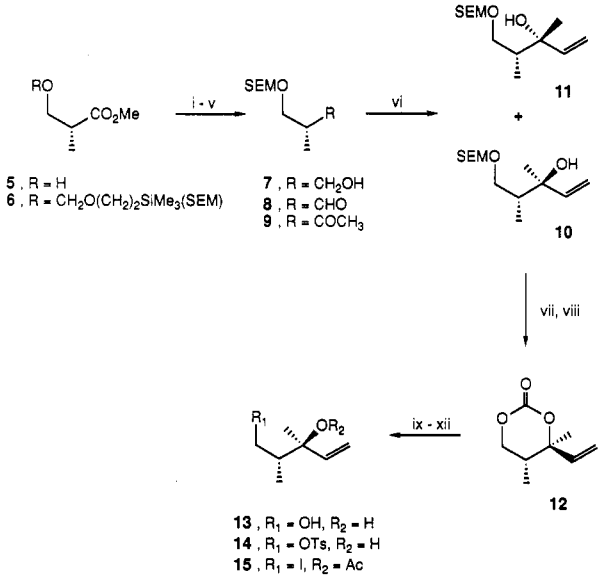
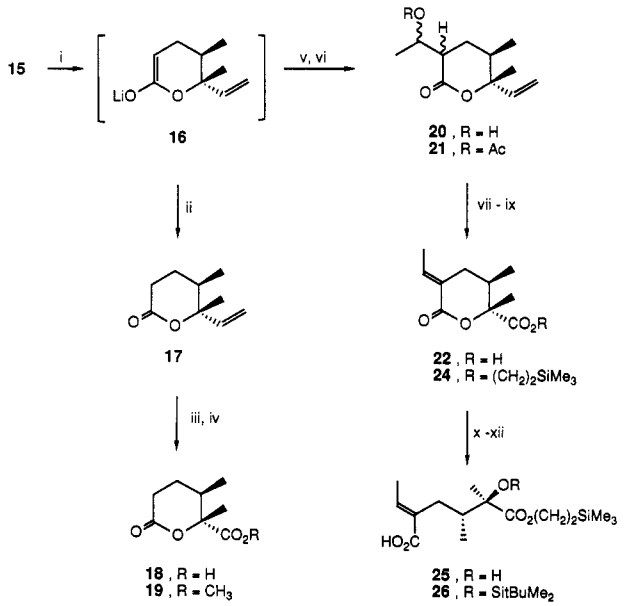


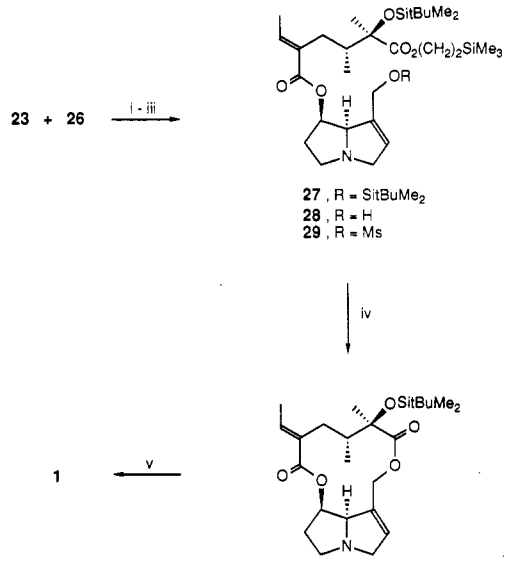
(i) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature (80%); (ii) $LiAlH_4$, Et_2O, room temperature; (iii) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, then Et_3N; (iv) MeMgBr, Et_2O; (v) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, then Et_3N (83% from **6**); (vi) CH_2=$CHMgBr$, THF, −78 °C, 1 h (93%); (vii) Bu_4NF, HMPA, 100 °C, 7 h (82%); (viii) $CO(Im)_2$, toluene, 90 °C, 18 h (84%); (ix) MeONa, MeOH, room temperature (90%); (x) TsCl, Py, room temperature; (xi) NaI, 2-butanone, reflux, 3 h (87% from **13**); (xii) Ac_2O, 3 equiv of DMAP, CH_2Cl_2, 0 °C (72%)

The transformation of **15** to lactone **17** was effected cleanly with lithium diisopropylamide, and subsequent oxidative cleavage of the vinyl group with ruthenium(IV)[8] then gave the carboxylic acid **18**. The methyl ester **19** of this acid has been prepared in racemic form by Narasaka et al.,[9] and a comparison of IR and NMR spectra of the two compounds corroborated our assignment of relative configuration. For the synthesis of integerrinecic acid lactone (**22**), the enolate **16**, acquired directly from **15**, was condensed with acetaldehyde and the resulting hydroxy lactone **20** was protected as the acetate **21**. Oxidative cleavage of the vinyl substitutent, followed by base-catalyzed elimination, furnished exclusively the *E* isomer **22**, the properties of which (including optical rotation) matched those reported.[10]



(i) 3.5 equiv of LDA, THF, −78 °C, 1 h; (ii) aq NH_4Cl (94%); (iii) cat. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (1:1:1.5), room temperature (73%); (iv) CH_2N_2; (v) CH_3CHO, −78 °C (87%); (vi) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, room temperature (90%); (vii) cat. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, room temperature; (viii) 3 equiv of DBU, CH_2Cl_2, room temperature, 20 h (68% from **21**); (ix) $Me_3Si(CH_2)_2OH$, 2-chloro-1-methylpyridinium iodide, Et_3N, room temperature (90%); (x) 1.2 equiv of LiOH, H_2O_2, THF/H_2O (2:1), room temperature (57%); (xi) *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C; (xi) $AcOH/THF/H_2O$ (3:3:1), room temperature (87% from **25**)

(+)-Retronecine (**4**) was obtained by basic hydrolysis of monocrotaline[11] and was selectively blocked at the primary hydroxyl group as the *tert*-butyldimethylsilyl ether **23**. For its union with **23**, **22** was converted to its (trimethylsilyl)ethyl ester **24** and the δ-lactone was hydrolyzed to hydroxy acid **25** as described previously.[3] The tertiary alcohol was then converted to *tert*-butyldimethylsilyl ether **26** (to prevent relactonization). In conformity with observations made by others,[3,4] esterification of the sterically hindered alcohol **23** with **26** required strenuous conditions which were met by activation of the latter as its acyl phosphate while **23** was converted to its lithium alkoxide. The confluence of these reactants produced ester **27**, from which the primary silyl ether was removed selectively to yield **28**. Conversion of **28** to mesylate **29** and selective



(i) $(EtO)_2POCl$, Et_3N, THF, room temperature, then **23**, BuLi, THF, cat. DMAP, room temperature (51% from **26**); (ii) NH_4F, MeOH, 60 °C (65%); (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iv) Bu_4NF, CH_3CN, room temperature (75%); (v) aq HF/CH_3CN (1:1), room temperature, 12 h (67%)

cleavage of the (trimethylsilyl)ethyl ester resulted in spontaneous intramolecular displacement to produce **30** in high yield. This exceptionally facile macrolactonization is to be contrasted with our unsuccessful efforts to construct **1** by translactonization of **31**,[12] prepared from **4** by esterification at the primary hydroxyl group with **22**.

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(9) Narasaka, K.; Uchimaru, T. *Chem. Lett.* **1982**, 57.

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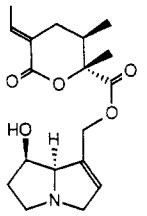
(11) Crout, D. H. G.; Davies, N. M.; Smith, E. H.; Whitehouse, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 671.

(12) Although we were eventually successful in procuring a macrolactone from **31**, this substance was clearly different from integerrimine (and senecionine). Spectral analysis confirmed that the structure of this product contained the integerrinecic acid moiety attached to retronecine in the reverse sense to that required for **1**, a result that can be interpreted via transesterification of **31** and subsequent translactonization.



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Finally, the silyl ether **30** was unmasked with hydrogen fluoride,[13] affording integerrimine which was identical by comparison of chromatographic behavior, spectral properties, and optical rotation[14] with the natural alkaloid.

Acknowledgment. We are indebted to Dr. C. C. J. Culvenor for a sample of natural integerrimine and to Dr. Koichi Narasaka, University of Tokyo, for IR and NMR spectra of **19**. Financial support was provided by the National Institute for Environmental Health Science (ES03334). Funds for the purchase of a Bruker AM 400 NMR spectrometer were provided by the National Science Foundation and the M. J. Murdock Charitable Trust.

Supplementary Material Available: Experimental details of **1**, **6**, **7**, **9**, **10**, **12–28**, and **30** (6 pages). Ordering information is given on any current masthead page.

(13) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(14) Integerrimine has $[\alpha]_D$ −18.3° (*c* 0.12, $CHCl_3$) and $[\alpha]_D$ +2.7° (*c* 1.1, MeOH).

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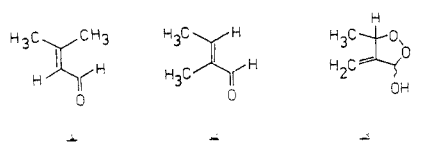
Received August 22, 1986

Diastereoselective Ene Reaction in the Photooxygenation of the Silyl Cyanohydrins of α,β-Unsaturated Aldehydes: Necessity for a Common Symmetrical Intermediate of the Perepoxide Type

Summary: The reaction of α,β-unsaturated aldehydes and their silyl cyanohydrin derivatives with singlet oxygen was studied. The latter showed a completely different pattern of reactivity and diastereoselectivity.

Sir: The present results (cf. Scheme I) on the photooxygenation of senecialdehyde (**1**) and tiglaldehyde (**2**) and their silyl cyanohydrins **1a,b** and **2a,b**, respectively, show that (i) while aldehyde **1** is inert toward $^1O_2$ even on prolonged exposure, aldehyde **2** affords exclusively the hydroxydioxolane **3**, the cyclic tautomer of the intermediary



allylic hydroperoxide [However, their silyl cyanohydrins **1a,b** and **2a,b**, respectively, react readily with singlet oxygen to give the ene-type products **4a,b** and **5a,b** from **1a,b** and **6a,b** and **7a,b** from **2a,b**], (ii) the regioselectivity is moderate (ca. 1:2) to low (ca. 1.3:1) for the conversions of **1a,b** into **4a,b** and **5a,b** and of **2a,b** into **6a,b** and **7a,b**, respectively [but for tiglaldehyde (**2**) the ene reaction takes place exclusively at the methyl group proximate to the carbonyl functionality[2]], and most importantly (iii) each regioisomer for a particular cyanohydrin is formed in the same diastereomeric ratio (dr), which is moderate (dr ~ 74:26) for **2a,b** and very high (dr > 96:4) for **1a,b**, i.e., *E*/*Z* ratios of **4a,b** are within experimental error equal to the threo/erythro ratios of **5a,b**.

A common symmetrical intermediate is essential in the formation of each of the pairs of regioisomers to account for these identical diastereoselectivities. We propose the perepoxide-like structures A and B as intermediates in the reaction of singlet oxygen with the silyl cyanohydrins **1a,b** and **2a,b**, respectively.

The required silyl cyanohydrins **1a,b** and **2a,b** were prepared from the aldehydes **1** and **2**, respectively, by treatment with the corresponding silyl chlorides (R = Me, *t*-Bu), KCN, and ZnI_2 in acetonitrile.[3] In the photooxygenations 0.2 M solutions of **1a,b** or **2a,b** in CCl_4 were irradiated externally with a 150-W sodium street lamp (Philips) at 0 °C and tetraphenylporphine (TPP) as sensitizer (5×10^{-4} M). The reaction progress was monitored by NMR and for 100% conversion ca. 6–8 h were necessary. The hydroperoxides **4–7** were isolated and purified by fractional distillation and/or silica gel chromatography and were characterized on the basis of their spectral (IR, ^1H and ^{13}C NMR) data. The proportion of regioisomers and for each the corresponding diastereomers were determined directly on the reaction mixture by means of 400-MHz ^1H NMR and 100-MHz ^{13}C NMR and are given in Scheme I (normalized to 100%). The silyl enol ethers **4a,b** proved to be sensitive toward photoisomerization during the photooxygenation. Thus, prolonged (ca. 24 h) irradiation resulted in a 6:1 photostationary mixture of *E*/*Z* isomers. A control experiment, employing a solution of K_2CrO_4 in methanol as UV filter, showed that immediately after complete conversion the *E* isomers of **4a,b** were produced predominantly (dr > 96:4) as the result of diastereomeric control.[4]

For such a high degree of diastereoselectivity to be observed, the enophilic attack of $^1O_2$ must be directed by intramolecular assistance through stereoelectronic effects and by diastereomeric differentiation through steric interaction. In regard to the stereoelectronic factor, it is significant to note that for the substrates **1a,b** the allylic hydrogen at the silyl cyanohydrin carbon suffers ene reaction, leading to enol ethers **4a,b**, while for the **5a,b** product a methyl hydrogen is abstracted by $^1O_2$. However, for substrates **2a,b** only methyl hydrogens participate in the ene reaction, affording the regioisomers **6a,b** and **7a,b** (Scheme I). Clearly the so-called cis effect[5] operates here, which for optimal intramolecular assistance directs the enophilic attack of $^1O_2$ preferentially to that side of the substrate which can align two allylic hydrogens perpendicular to the olefin plane and flanking the terminal oxygen atom. For substrate **1a,b** this stereoelectronic guidance

(1) Humboldt, A. v. Postdoctoral Fellow, 1984–1986.

(2) (a) Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (b) Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1985**, *26*, 5991. (c) Adam, W.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070.

(3) (a) Rawai, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275. (b) Albright, D. *Tetrahedron* **1983**, *39*, 3207.

(4) The olefinic protons in **4a,b** are shifted for the *E* isomers ca. 0.13 ppm downfield relative to the *Z* isomers (cf. Hertenstein, U.; Hünig, S.; Reichelt, H.; Schaller, R. *Chem. Ber.* **1982**, *115*, 261), so that a rigorous stereochemical assignment of the *E* and *Z* pairs of **4a,b** was possible; the stereochemical assignment of the threo,erythro pairs **5a,b** was inferred from the *E*, *Z* pair **4a,b**, but a rigorous proof is in progress.

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