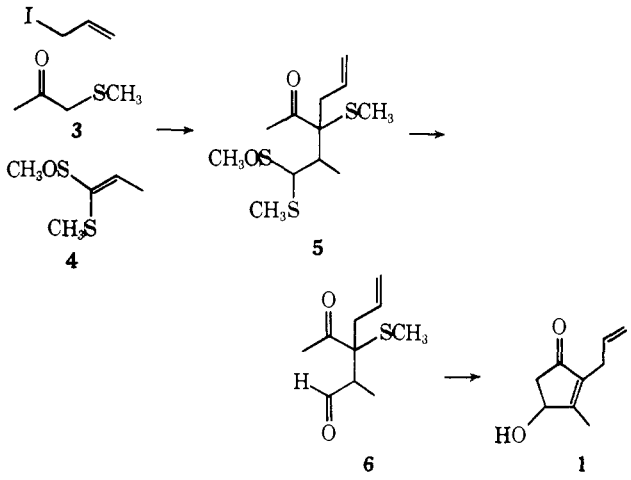
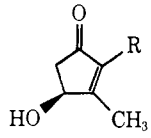


overall yield) which was identical in all respects with authentic *dl*-allethrolone.[9]

The same reaction sequence starting with ketone **3** and sulfoxide **4** but using *cis*-1-iodo-2-butene[10] as the alkylating agent gave pure *dl-cis*-cinerolone (**2**) in 75% overall yield.[9] Rethrolones **7** and **8** may also be prepared in this manner using either methyl iodide or *trans*-1-iodo-2-butene. The overall yields of pure **7** and **8** were 80 and 75%, respectively.



1, R = $CH_2CH{=}CH_2$
2, R = *cis*-$CH_2CH{=}CHCH_3$
7, R = CH_3
8, R = *trans*-$CH_2CH{=}CH_3$

The generality of this reaction sequence is currently being explored with respect to the construction of hydroxycyclopentenone systems that have been converted into the prostaglandins.[11]

Acknowledgment. We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Hoffmann-LaRoche Company, Nutley, N. J., for support of this work.

(9) We thank Drs. W. Leimgruber and R. Kierstead of the Hoffmann-La Roche Company, Nutley, N. J., for samples and spectra of allethrolone and *cis*-cinerolone. The overall yields quoted for each of the four rethrolones reported herein are based on isolated and pure material.

(10) Prepared by the same method used by S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953) for the preparation of *trans*-1-iodo-2-butene.

(11) For examples, see A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 9256 (1972), and references cited therein.

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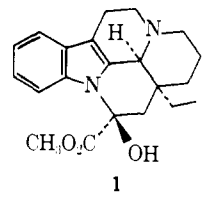
A High Yield Stereospecific Total Synthesis of Vincamine

Sir:

Vincamine is a pentacyclic indole alkaloid first isolated from *Vinca minor* L. (*Apocyanaceae*) by Schlittler.[1] The alkaloid has exhibited significant antihypertensive and sedative activity and as a result has been the object of considerable synthetic effort.[2] Herein we describe a stereospecific total synthesis of *dl*-vincamine (**1**), the salient features of which include:



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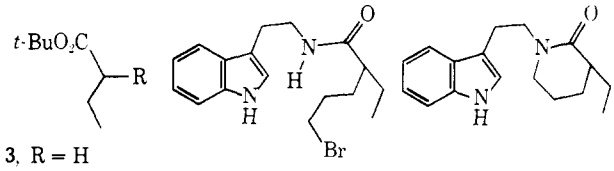
(a) a new high yield construction of the tricyclic lactam **2**,[3] (b) regiospecific reaction of the dianion derived from **2** with an electrophilic equivalent of methyl pyruvate,[4] (c) realization of the synthetic objective in 43% overall yield starting from *tert*-butyl butyrate.

The intermediate lactam **2** was prepared by alkylation of the lithium enolate of *tert*-butyl butyrate (**3**) with 1,3-dibromopropane to give the bromo ester **4** in 90% yield (bp 55°, 0.2 Torr).[5] Compound **4** was converted into the bromoamide **5** in 80% overall yield by the following reaction sequence. Treatment of **4** with *p*-toluenesulfonic acid (10% by weight) in refluxing benzene (1 *M*) gave the corresponding bromo acid which without purification was converted into its acid chloride analog with oxalyl chloride (1.3 equiv) in benzene (0.5 *M*). The crude acid chloride was then treated with a mixture of hydrochloride (1 equiv) and lithium hydride (2.5 equiv) in THF solution (1 *M*) to give the amide **5** (mp 102°).[6] Reaction of **5** with potassium hydride (10 equiv) in THF solution (1 *M*) gave the lactam **2** in 95% yield (mp 124–125°, lit. 124–126°).[3]



3, R = H
4, R = $(CH_2)_3Br$

5 **2**

Addition of **2** (1 equiv) at −78° to a solution of lithium diisopropylamide (2.1 equiv, 1 *M* in THF) gives rise to the dianion **6** (tan suspension). Treatment of the dianion with methyl 2-thiomethylacrylate[7] (1.1 equiv) followed by stirring at −78° for 1.5 hr affords the lactam ester **7** (mp 90–95°)[8] in quantitative yield.

(1) E. Schlittler and R. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953).

(2) (a) L. Szporny and K. Szasz, *Arch. Exp. Pathol. Pharmakol.*, **236**, 296 (1959); (b) M. E. Kuehne, *J. Amer. Chem. Soc.*, **86**, 2946 (1964); (c) K. H. Gibson and J. E. Saxton, *Chem. Commun.*, 1490 (1969); (d) M. C. Thal, T. Sevenet, H. P. Husson, and R. Rotier, *C. R. Acad. Sci., Ser. C*, **275**, 1295 (1972); (e) C. Szantay, L. Szabo, and G. Kalaus, *Tetrahedron Lett.*, 191 (1973).

(3) Lactom **2** has been prepared by E. Wenkert and B. Wieckberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965), in 12% overall yield starting from diethyl ethylmalonate.

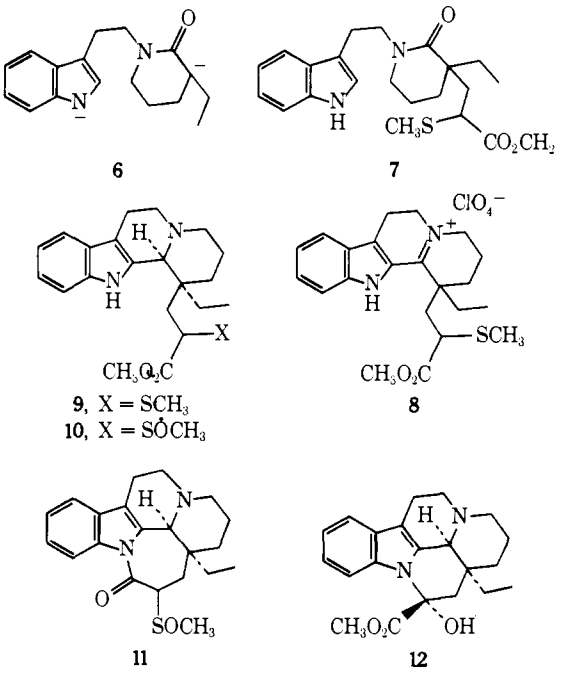
(4) R. J. Cregge, J. L. Hermann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973).

(5) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).

(6) All new compounds exhibited satisfactory spectral and physical properties.

(7) A convenient and high yield preparation of this compound is described by K. D. Gundermann and H. Schulze, *Chem. Ber.*, **94**, 3254 (1961). For examples of the reactions of this compound with nucleophiles see ref 4.

(8) Lactam **7** consists of a mixture of two epimeric materials which may be separated by liquid chromatography into compounds melting



Cyclization of **7** (1 equiv) was carried out in refluxing acetonitrile (0.1 M) containing phosphorus oxychloride (30 equiv) for 14 hr. The crude reaction mixture was treated with lithium perchlorate (2 equiv) in water to give the immonium perchlorate **8** (mp 88–96°, 93% yield from **7**). Stereospecific reduction of **8** to the tetracyclic amine ester **9** (mp 102–104°) could be realized in 98% yield using lithium tri-*tert*-butoxyaluminum hydride (3.0 equiv) in THF solution (0.3 *M*) at 0°.[9]

The final ring of vincamine was introduced by oxidation of **9** (1 equiv) to the sulfoxide **10** (mp 110–115°, 96% yield) with *m*-chloroperbenzoic acid (1.3 equiv) in methylene chloride solution (0.1 *M*). Treatment of **10** (1.0 equiv) with sodium hydride (2 equiv) in THF solution (0.1 *M*) gave the lactam sulfoxide **11** (mp 75–77°) in 98% yield. Direct conversion of **11** into vincamine may be accomplished by reaction of the lactam sulfoxide (1.0 equiv) with acetyl chloride (2.2 equiv) at 0° for 20 min followed by addition of sodium methoxide (4.0 equiv) in methanol (0.1 *M*).[10] After stirring 14 hr at 22°, dilution of the reaction mixture with water gave pure *dl*-vincamine (**1**) (mp 225–227°) in 80% yield.[11] The same reaction using 2.5 equiv of sodium methoxide in methanol for 6 hr afforded pure *dl*-epivincamine (**12**) (mp 203–204°) in 85% yield.[12]

at 105–106° and 82–83°. The epimeric mixture was used in the actual synthesis thus accounting for the melting point ranges reported for compounds **7** to **11** inclusive.

(9) Sodium borohydride reduction of **8** gave a mixture of *cis* and *trans* isomers of **9** (4:1) which are easily separated by liquid chromatography. Less than 0.5% of the *trans* isomer of **9** is formed when lithium tri-*tert*-butoxyaluminum hydride is used.

(10) Presumably this reaction sequence involves acid chloride induced rearrangement of the sulfoxide functionality into the α-acetoxysulfide followed by methoxide conversion of this intermediate into its α-keto lactam analog. Ring opening of the lactam with methoxide affords the corresponding methyl pyruvate derivative which is known to undergo ring closure into vincamine (ref 2e).

(11) We thank Professor M. P. Cava, Department of Chemistry, University of Pennsylvania for a sample of naturally occurring *dl*-vincamine. The synthetic *dl*-vincamine was identical in all respects to the natural material.

(12) Epivincamine is apparently a kinetic product in this reaction since prolonged refluxing or the use of excess methoxide quantitatively converts epivincamine into vincamine. A similar experiment is described in ref 2e.

Use of the dianion **6** as an intermediate in the synthesis of other indole alkaloids is currently under investigation.

Acknowledgment. We thank the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Hoffmann-LaRoche Company, Nutley, N. J., for support of this work.

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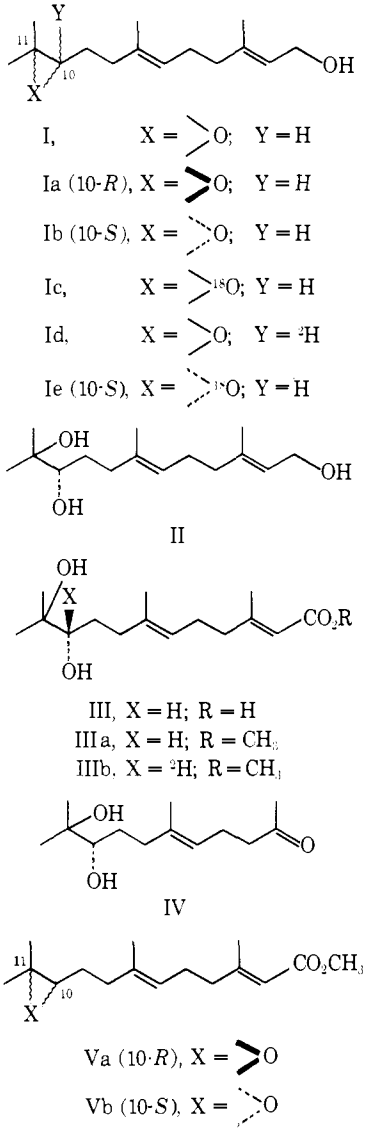
Trans and Cis Hydration of Racemic 10,11-Epoxyfarnesol into Optically Active Glycols by Fungus

Sir:

We have recently established the fungal transformation of a racemic mixture of 10,11-epoxyfarnesol (I)



into three optically minus glycollic metabolites, *i.e.*, (*S*)-(−)-10,11-dihydroxyfarnesol (II), (*S*)-(−)-10,11-di-