proached here unitropic, in contrast to the ditropic pattern described previously. The reaction of such a crystal is shown in Figure 3.

These results provide support for the mechanism of the reaction previously proposed.[1-3] Ammonia attack at a carboxyl group leads to disorientation of the molecules nearby and permits diffusion of additional ammonia molecules to penetrate to a further carboxyl group. The hydrogen-bonded chains provide a much-preferred reaction path through the crystal. It will be noted that tongues of reaction preceeding the general front visible in Figure 3 suggest that reaction is accelerated by crystal imperfections in certain regions. Examination of the crystal structure shows that each carboxyl–carboxyl hydrogen-bonded center is surrounded by an assembly of cyclopropyl, phenyl, and methyl groups which could be expected to slow migration of ammonia molecules in any direction except the two opposing directions parallel to the *b* axis. Along *b* the spacing of carboxyl hydrogen-bond centers is only 3.2 Å. Although this is substantially less than the closest spacing of about 3.8 Å in many acids with the cyclic hydrogen-bonded dimer structure, it may be noted that in this case only a single new carboxyl group is exposed with each 3.2 Å of travel whereas two carboxyl groups are exposed each 3.8 Å in the reaction of cyclic dimers.

It appears likely that studies of this kind can be expected to lead to knowledge of the mechanisms of solid–gas reactions which should assist in utilizing (or preventing) such reactions and also can give rapid information about the internal structure of crystals. See paragraph at end of paper regarding supplementary material.

Acknowledgment. The authors would like to thank the National Science Foundation (Grant GH-33634) for support of this work. Dr. A. H.-J. Wang assisted with several aspects of the crystal structure study.

Supplementary Material Available. A table of atomic coordinates will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St. N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-3699.

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A New and Highly Efficient Synthesis of Rethrolones

Sir:

Allethrolone (**1**) and *cis*-cinerolone (**2**) are examples of a class of hydroxycyclopentenones commonly called rethrolones. These substances occur in nature as the alcohol moiety of the pyrethrins, a group of esters derived from either chrysanthemic or pyrethric acids.[1] Pyrethrins are biodegradable and exhibit high insect toxicity but low mammalian toxicity.[2] These manifold properties have led to intense interest in the synthesis of pyrethrins and preparative routes to both chrysanthemic acid and the rethrolones have been developed.[3] We wish to describe a highly efficient general construction of rethrolones *via* a one-step conjugate addition alkylation reaction which affords intermediates containing all of the carbon atoms and appropriate functionality for simple conversion into either **1** or **2**.

The construction of allethrolone as well as the other rethrolones described herein was carried out in the following manner.[4] A solution of thiomethylacetone (**3**)[5] (1 equiv) dissolved in THF (1 *M*) was treated with sodium hydride (1.15 equiv) at 0°. To this solution was added the ketene thioacetal monoxide, **4**[6] (1 equiv), and the resulting mixture was stirred at 0° for 5 hr. Allyl iodide (1.15 equiv) was added and the reaction mixture was then allowed to stir 16 hr at 0°. Work-up in the usual manner gave a yellow oil (99% yield) which was readily identified as compound **5** on the basis of its spectral characteristics.[7] Hydrolysis of **5** (1 equiv) in acetonitrile (1 *M*) using 70% perchloric acid (0.3 equiv) at 0° for 2 hr gave the keto aldehyde **6** (99% yield).[8] Conversion of **6** into allethrolone was accomplished by treatment of the keto aldehyde (1 equiv) with potassium *tert*-butoxide (1 equiv) in *tert*-butyl alcohol (1 *M*) at 22° for 15 min. Chromatography of the crude reaction mixture gave pure *dl*-allethrolone (80% yield, 78%

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(2) M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and B C. Pearson, *Nature (London)*, **213**, 493 (1967); M. Elliott, N. F. Janes, and B. C. Pearson, *J. Chem. Soc. C*, 2551 (1971); Y. Katsuda, T. Chikamoto, H. Ogami, H. Hirobe, and T. Kunishige, *Arg. Biol. Chem.*, **33**, 1361 (1969).

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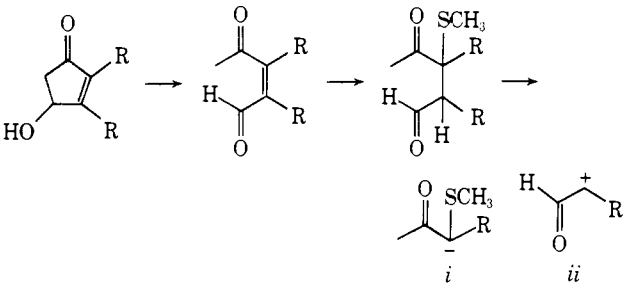
(4) This synthetic strategy arose from the following antithetic transformations which ultimately led to the ketone enolate i and the enolonium ion ii.

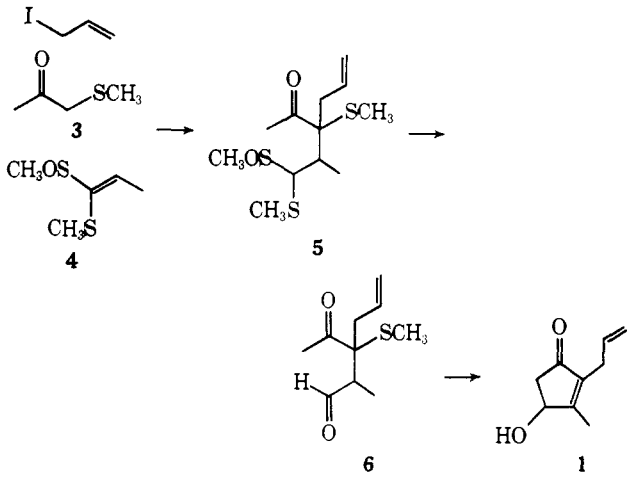


(5) C. K. Bradsher, F. C. Brown, and R. J. Grantham, *J. Amer. Chem. Soc.*, **76**, 114 (1954).

(6) J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.*, 4707 (1973).

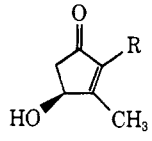
(7) Infrared ($CHCl_3$) 1687 (C=O), 1632 (C=C), 1032 cm^{-1} (S=O). The nmr and mass spectra are also in satisfactory agreement with the structure assigned to compound **5**. The reaction leading to **5** was worked-up with saturated ammonium chloride solution (pH 6).

(8) Infrared ($CHCl_3$) 1712, 1692, (C=O), 1637 cm^{-1} (C=C); nmr (100 MHz, $CDCl_3$) δ 10.16 (s, 1 H); mass spectrum *m/e* 200.



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 pre-



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

pared 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.

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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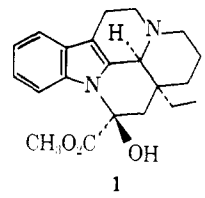
A High Yield Stereospecific Total Synthesis of Vincamine

Sir:

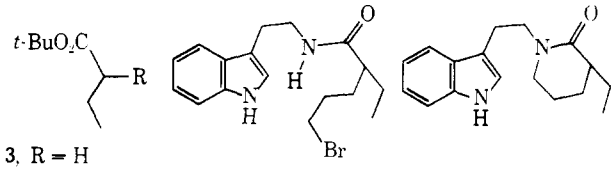
Vincamine is a pentacyclic indole alkaloid first isolated from *Vinca minor* L. (*Apocyanaceae*) by Schlittler.[1] The alkaloid has exhibited significant antihypertensive and sedative activity and as a result has been the object of considerable synthetic effort.[2] Herein we describe a stereospecific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



1

(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 follow-



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

5 **2**

ing 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]

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