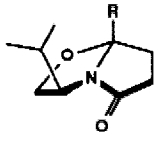
Tetrahedron Letters,Vol.30,No.14,pp 1745-1748,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# CHIRAL BICYCLIC LACTAMS. AN ASYMMETRIC SYNTHESIS OF CIS-(1S, 3R) DELTAMETHRINIC ACID

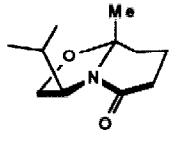
A. I. Meyers* and Daniel Romo
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523 USA

**Summary** - Cyclopropanation of a chiral α,β-unsaturated bicyclic lactam derived from *tert*-leucinol and levulinic acid gave after 4 steps, the title compound in > 99% ee.

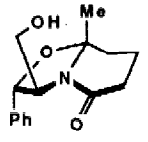
We have recently described the synthetic utility of chiral bicyclic lactams **1-3**, as precursors to a variety of enantiomerically pure quaternary carbon compounds.[1] Furthermore, a novel asymmetric cyclopropanation based on these bicyclic lactams has also appeared from




1 (R = Ph, Me)

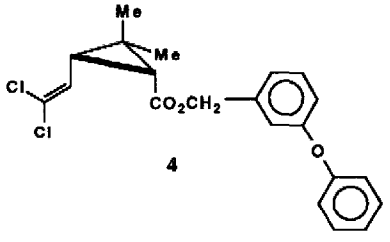



2

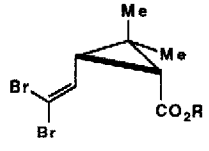


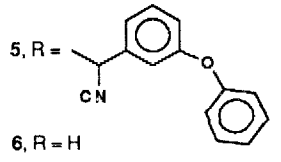

3

these laboratories.[2] As a result of these successes, we have now turned our attention to an efficient entry into the insecticidal substances derived from natural pyrethroids, an important class of agricultural agents due to their low mammalian toxicity and biodegradability.[3] In this armory of pest control substances are two pyrethroid analogs, cypermethrin **4** and deltamethrin




4



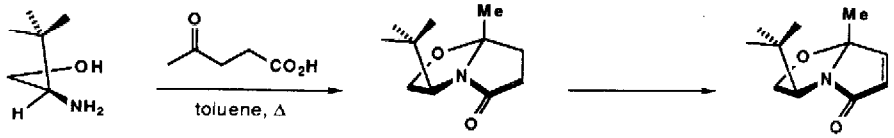




6, R = H

**5** which are in wide commercial use because of their photostability and high insecticidal activity.[4] The efficacy and level of activity of these substances is highly dependent upon the relative and absolute stereochemistry about the cyclopropane ring. In the case of **5**, the most

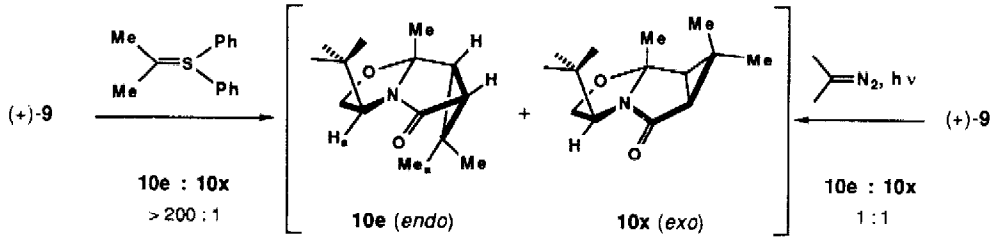
potent commercial insecticide, the greatest activity is exhibited by the *cis*-(1R, 3S) configuration.[5] Although a number of syntheses of deltamethrinic acid **6** have been reported, primarily aimed at cyclopropanation reactions,[4b] only very few synthetic routes have been either enantioselective[4b,6] or asymmetric.[7,8]

For the first time in these studies, we introduce the bicyclic lactam **8**,[9] obtained in 92% yield from *t*-leucinol **7**[10] and levulinic acid, by azeotropic removal of water. The unsaturation



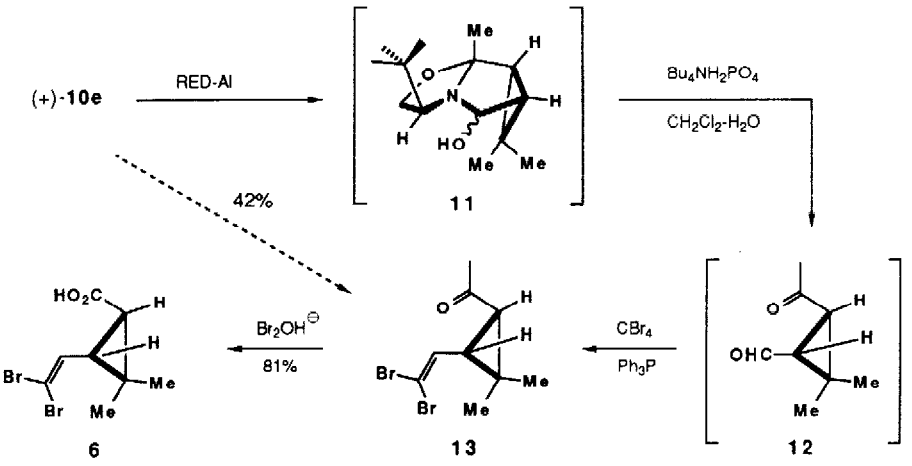

**7** **8** **9**

was introduced by metalation (LDA, -78° C, THF), selenation (PhSeBr, -78° C, 4 h), and oxidation with hydrogen peroxide to give **9** in 75-80% yield.[11] Cyclopropanation of **9** was performed in two fashions. The first was treatment of **9** with 2.0 equiv of diphenylsulfonium




isopropylide[12] which gave the *endo* product **10e** in 94% yield.[13] The *exo*-diastereomer, **10x**, could not be detected (vpc) and our limits of detection were estimated at .05%. However, when diazoisopropane[14] was added to (+)-**9** ($Et_2O$, 25° C, 19 h) and the intermediate pyrazolines were irradiated (UV lamp, 4 h), an 88% yield of **10e-10x** was obtained as a 1:1 mixture (vpc). The structural assignment of **10e** was conveniently determined by homonuclear NOE studies which showed enhancement of $H_a$ when the *syn*-methyl ($Me_a$) was irradiated. The *endo*-addition is also consistent with earlier work from our laboratory.[2]

The synthesis of deltamethrinic acid **6** continued by reduction of **10e** using Red-Al (0.7 eq, THF, 25° C) which furnished the carbinolamine **11**. This intermediate was directly subjected to hydrolysis with tetrabutyl ammonium dihydrogen phosphate ($CH_2Cl_2$-$H_2O$, 1:1, 96 h, 25° C). The resulting keto-aldehyde **12** is quite volatile and in order to avoid losses, the crude material was immediately treated with the orange triphenyl phosphine-$CBr_4$ reagent reported by Ramirez.[15] The dibromo olefin **13** was, therefore, isolated pure in 42% overall yield[16] from the lactam **10e**. Finally, haloform reaction[17] of the methyl ketone using bromine-sodium hydroxide




(-10° C, 4 h, then reflux 1 h) gave *cis* -(1S, 3R)-**6** in 81% yield; mp 129-130°, $[\alpha]_D^{22}$ -16.8° (c 1.5, $CHCl_3$). Comparison with an authentic sample (mp 129-132°, $[\alpha]_D^{22}$ 17.3°, c 1.5, $CHCl_3$) obtained from Rousell-Uclaf showed that the synthetic material from this study was well within acceptable limits.[18] From the sign of rotation of **6**, it may also be concluded that the addition of the sulfur ylide to **9** proceeded from the *endo* face. Due to the use of L(S)-*t*-leucinol, we reached the optical antipode of the commercial material. Undoubtedly, use of D(R)-*t*-leucinol would lead to the correct enantiomer.

This asymmetric cyclopropanation process is quite general and a detailed account will be reported in due course.

**Acknowledgment**. Financial aid for this work was provided by the National Institutes of Health and the National Science Foundation. An NSF Predoctoral Minority Fellowship (to DR) is gratefully acknowledged. We thank Professor A. Krief (Namur) for spectral data on **6** and Dr. J-O Demoute (Roussel-Uclaf) for an authentic sample of **6**.

## References

1. Meyers, A. I.; Lefker, B. A. *Tetrahedron*, **1987**, *43*, 5663 and references cited therein.
2. Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245.
3. Burt, P. E.; Elliot, M.; Farnam, A. W.; Janes, N. F.; Needham, P. H.; Pulman, P. A. *Pestic. Sci.* **1975**, *6*, 537.
4. For reviews see a) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.*, **1978**, *7*, 473; b) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 703. c) Nauman, K. "*Chemie der Synthetischen Pyrethroid Insektizide*", Springer-Verlag, Berlin, 1981.
5. Elliot, M. *Pestic. Sci.* **1980**, *11*, 119.

6. For recent advances in enantioselective syntheses derived from (+)-3-carene, see Mandel, A. K. et al. *Tetrahedron*, **1986**, *42*, 5715.
7. Kleschick, W. A.; Reed, M. W.; Bordner, J. *J. Org. Chem.* **1987**, *52*, 3168.
8. Krief, A.; Dumont, W.; Pasau, P. *Tetrahedron Lett.* **1988**, *29*, 1079.
9. Mp 59.0-60.0° C, $[\alpha]_D^{22}$ 114° (c 1.1, EtOH). This and all other new compounds gave satisfactory spectral, mass, and combustion data.
10. We are grateful to Dr. K. Drauz and Dr. H. Lotter of DeGussa A.G., Hanau, West Germany for a generous gift of this material. This can also be prepared by reduction of *t*-leucine (DeGussa) with $LiAlH_4$ in THF.
11. Mp 54-55° C, $[\alpha]_D^{22}$ 68.4° (c 1.1, EtOH).
12. Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2328; Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.
13. Mp 76.0-77.0° C, $[\alpha]_D^{22}$ 100.9° (c 1.1, EtOH).
14. Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Org. Syn.* **50**, 27.
15. Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
16. Mp 40.5-41.0° C, $[\alpha]_D^{22}$ 24.0° (c 0.9, $CHCl_3$). A slight deficiency of hydride was employed in the reduction of **10e**. If equimolar or excess hydride was used, over-reduction of **11** was observed. As a result of this, the yield of dibromo olefin **13** is based on recovered **10e**.
17. Sandborn, L. T.; Bousquet, E. W. *Org. Syn. Coll. Vol. 1*, 526.
18. A more accurate measure of the enantiomeric purity of **6** is based on the diastereomeric purity of **10e** (> 99% de *via* vpc).

(Received in USA 22 December 1988)