Tetrahedron Letters,Vol.30,No.22,pp 2941-2944,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

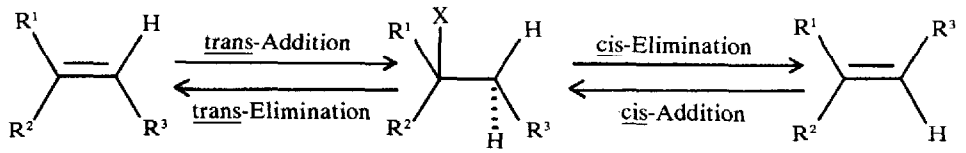
STEREOSELECTIVE ISOMERIZATION OF ETHYLIDENE LACTAM FOR THE SYNTHESIS OF (±)-Z-ISOSITSIRIKINES

Takeaki Naito,* Tetsuro Shinada, Okiko Miyata, and Ichiya Ninomiya
Kobe Women's College of Pharmacy, 4-19-1, Motoyamakita, Higashinada, Kobe 658, Japan

Summary: Smooth isomerization of stable E-ethylidene group into the unstable Z-isomer was facilitated in the case of the ethylidene lactams **2** and **6**, and provided the total synthesis of Z-isositsirikines **7-10**.

Stereoselective preparation of trisubstituted olefins has attracted much attention of synthetic organic chemists.[1-4] Theoretically, trans-addition of an appropriate additive to the trisubstituted olefins coupled with cis-elimination of the adduct or cis-addition and trans-elimination would furnish the isomerized olefins from either E- or Z-isomer.

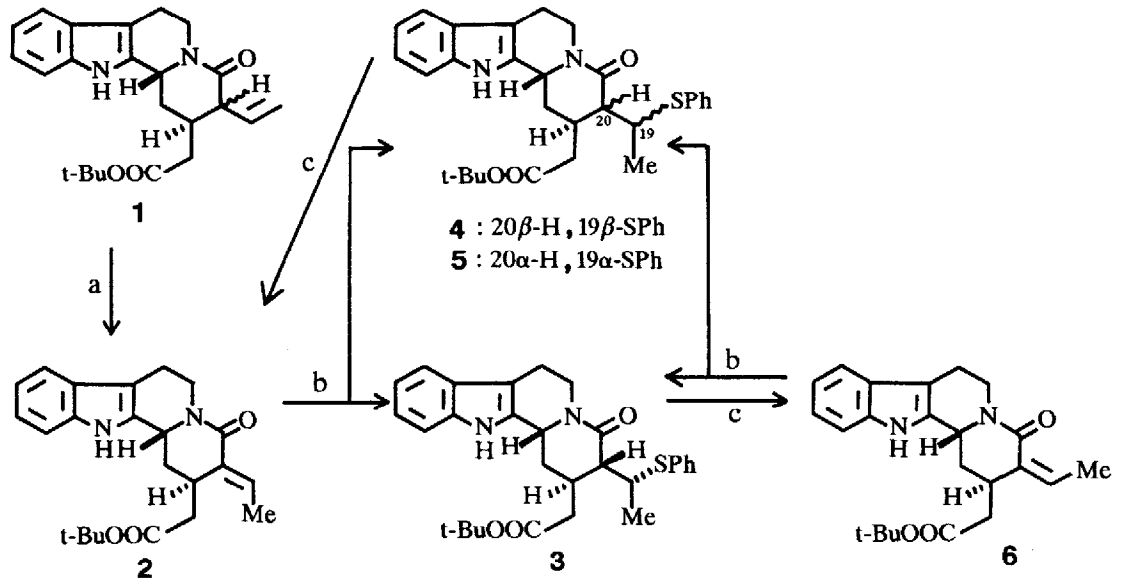
This idea has now been visualized in the ethylidene lactam systems in which thiophenol was stereoselectively added to the α,β-unsaturated lactam in the trans manner and then eliminated stereoselectively via cis-elimination of the resulting sulfoxide.[5] The utility of this method is demonstrated by the stereoselective synthesis of both E- and Z-isositsirikines of monoterpenoid indole alkaloids.



E Z

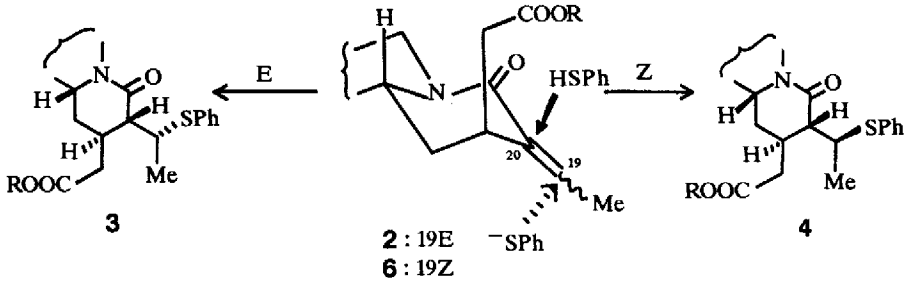
The known vinyllactam **1**[6] was readily converted into the (19E)-ethylidene lactam **2**[7] as a sole product in 89 % yield by treatment with sodium hydride. The result shows that the (19E)-ethylidene lactam **2** is more stable than the (19Z)-ethylidene lactam **6** presumably due to the absence of steric repulsion between a lactam carbonyl and terminal methyl groups in **2**. Treatment of the (19E)-lactam **2** with 3 equiv. of lithium thiophenoxide[8] in the presence of 3 equiv. of thiophenol in tetrahydrofuran at 70 °C gave stereoselectively the trans-adduct **3**[9] in 86 % yield in addition to the cis-adduct **4**[10] in only 6 % yield. Oxidation of **3** with

m-chloroperbenzoic acid followed by pyrolysis of the resulting sulfoxide[11] in boiling toluene gave exclusively the desired (19Z)-lactam **6**[12] in 95 % yield, while the minor adduct **4** upon similar treatment reverted back to the starting **2** in good yield. Furthermore, similar addition-elimination reaction was successfully applied to the (19Z)-lactam **6** for its stereoselective conversion into **2**. Treatment of **6** with lithium thiophenoxide in the presence of thiophenol in tetrahydrofuran at 70°C gave three adducts **3**, **4**, and **5**[13] in 10, 53, and 10 % yields respectively, of which the latter two adducts **4** and **5** were converted into the identical **2** by pyrolysis of the corresponding sulfoxides in good yields.



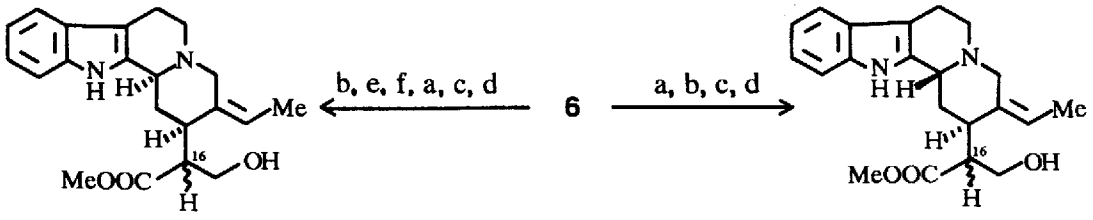
a) NaH-THF ; b) PhSLi-PhSH-THF ; c) i. m-CPBA, ii. Δ

These selectivities for the predominant formations of the trans-adduct **3** from the (19E)-lactam **2** and the trans-adduct **4** from the (19Z)-lactam **6** can be explained as follows. Lithium thiophenoxide attacks at the 19-position of the α,β-unsaturated lactams **2** and **6** from the less hindered α-side and subsequent protonation takes place predominantly from β-side as a result of the Michael trans-addition.[14]



Thus, we have now succeeded in the synthetically useful interconversion between **2** and **6**, though one-way conversion of **6** into **2** has been illustrated by Winterfeldt's group.[15]

This newly developed isomerization reaction has been successfully applied to the stereoselective total synthesis of Z-isositsirikine group of alkaloids, (±)-Z-isositsirikine (**7**),[16,18] (±)-16-epi-Z-isositsirikine (**8**)[17,18] and also two unnatural hydroxyesters **9** and **10**. Thus, by a series of reactions[6] including reduction of the lactam carbonyl group, transesterification, formylation, and finally reduction of the formyl group, the lactam **6** was successfully converted into the hydroxyesters **9** and **10** and (±)-Z-isositsirikine (**7**) and (±)-16-epi-Z-isositsirikine (**8**).



a) AlH_3 ; b) MeOH-H_2SO_4 ; c) LDA-HCOOEt ; d) $NaBH_4$; e) O_2-$Cu(OAc)_2$-TFA ; f) $NaBH_4$-AcOH

In conclusion, we have now established the synthetically useful method for the stereoselective construction of both Z- and E-ethylidene compounds[6] and succeeded in the total syntheses of all eight stereoisomers of isositsirikine group of alkaloids.

ACKNOWLEDGEMENT

We wish to thank the Ministry of Education, Science and Culture (Japan) for the grant in aid to this research.

REFERENCES AND NOTES

1. D. J. Faulkner, Synthesis, **1971**, 175.
2. J. Bosch and M. L. Bennasar, Heterocycles, 1983, **20**, 2471.
3. T. A. Blumenkopf and L. E. Overman, Chem. Rev., 1986, **86**, 857.
4. W. C. Still and C. Gennari, Tetrahedron Lett., 1983, **24**, 4405.
5. S. Oae and N. Furukawa, Tetrahedron, 1977, **33**, 2359.
   Isomerization of E-nitroolefins to Z-counterparts involving the addition-elimination reaction of a seleno group has been shown by Kaji's group.
   N. Ono, A. Kamimura, T. Kawai, and A. Kaji, J. Chem. Soc., Chem. Commun., **1987**, 1550.
6. T. Naito, T. Shinada, O. Miyata, and I. Ninomiya, Heterocycles, 1988, **27**, 1603.
7. **2**:^{1}H NMR($CDCl_3$)δ: 7.08 (1H, q, J= 7 Hz, 19-H) and 1.86 (3H, d, J= 7 Hz, 19-Me).
8. H. Niwa, Y. Uosaki, and K. Yamada, Tetrahedron Lett., 1983, **24**, 5731.
9. **3**:MS m/z: 490 (M^+);^{1}H NMR($CDCl_3$)δ: 3.86 (1H, qd, J= 7 and 5 Hz, 19-H), 2.53 (1H, br d, J= 5 Hz, 20-H), and 1.42 (3H, d, J= 7 Hz, 19-Me).
10. **4**:MS m/z: 490 (M^+);^{1}H NMR($CDCl_3$)δ: 4.12 (1H, qd, J= 7 and 3.5 Hz, 19-H), 2.43 (1H, br t, J= 3.5 Hz, 20-H), and 1.17 (3H, d, J= 7 Hz, 19-Me).
11. Diastereoisomeric 1:1 mixture of two sulfoxides was readily separated by medium-pressure column chromatography but their stereostructures have not been established yet. One polar sulfoxide took 1 h for the complete pyrolysis and the other less polar one, 2 h respectively, affording the identical (19Z)-ethylidene lactam **6** in 98-99 % yield.
12. **6**:^{1}H NMR($CDCl_3$)δ: 6.06 (1H, q, J= 7 Hz, 19-H) and 2.17 (3H, d, J= 7 Hz, 19-Me).
13. **5**:MS m/z: 490 (M^+);^{1}H NMR($CDCl_3$)δ: 3.93 (1H, qd, J= 7 and 4.4 Hz, 19-H), 2.71 (1H, t, J= 4.4 Hz, 20-H), and 1.49 (3H, d, J= 7 Hz, 19-Me).
14. W. E. Truce and A. J. Levy, J. Am. Chem. Soc., 1961, **83**, 4641.
15. R. Freund and E. Winterfeldt, Liebigs Ann. Chem., **1988**, 1007.
16. W. Kohl, B. Witte, W. S. Sheldrich, and G. Höfle, Planta Medica, **1984**, 48.
17. S. Mukhopadhyay, A. El-Sayed, G. A. Handy, and G. A. Cordell, J. Nat. Prod., 1983, **46**, 409.
18. E. Winterfeldt and R. Freund, Liebigs Ann. Chem., **1986**, 1262.

(Received in Japan 1 March 1989)