COMMUNICATION

Shikimic acids from furan; methods of stereocontrolled access to 3,4,5-trioxygenated cyclohexenes

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Oxabicycloheptenes **1** and **2** are converted to 3,4,5-oxygenated cyclohexenes by stereocontrolled hydroxylations and epoxidations coupled with reverse-Michael cleavage of the oxabicyclo system. Three epimers of shikimic acid are synthesized by these methods.

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On a transformé les oxabicycloheptènes **1** et **2** en cyclohexènes oxygénés en positions-3,4,5 grâce à des hydroxylations et des époxydations stéréocontrolées couplées à une scission de type rétro-Michael du système oxabicyclique. On a synthétisé trois épimères de l'acide shikimique par ces méthodes.

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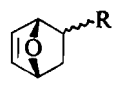
In a current paper (1) we report the general occurrence of some 5-*endo-trig* reversals of 7-oxabicyclo[2.2.1]heptenes and provide a stereoelectronic rationale for the violations of Baldwin's Rules (2) observed in these cases. The reverse-Michael reactions (1, 3) of such compounds, coupled with standard epoxidations and hydroxylations, offer significant opportunities for the generation of multi-oxygenated cyclohexenes with virtually complete control of stereochemistry. We illustrate herein the application of these procedures to the efficient synthesis of some shikimic acids (4).[2]

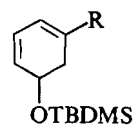
Oxabicycloheptenes **1** and **2**, easily obtained from furan (5), were employed as starting materials. Conversion (1) of cyanide **2** to cyclohexadiene **3** followed by osmylation (osmium tetroxide/pyridine) produced diol **4** with complete regio and stereoselectivity. There is little doubt that the bulky TBDMS group is responsible for directing hydroxylation from the lower face of the 3,4 double bond. The synthesis of (±) shikimic acid **5** was then completed by the standard procedures of desilylation (tetrabutylammonium fluoride/THF) and alkaline hydrolysis in 31% overall yield from **2**.

If the osmylation is conducted before the reverse-Michael fission, the stereochemistry of the *cis*-diol function thereby introduced is reversed and 5-epishikimic acid should result. Accordingly, bicyclo ester **1** was osmylated as before and the resulting *exo*-diols **6** converted to the acetonides **7**. Reverse-Michael cleavage of the latter (LDA, THF, 0°C) provided the expected cyclohexenol **8** (86%). Hydrolysis of the acetonide (aqueous acetic acid, 16 h, 20°C) and saponification produced (±) 5-epishikimic acid **9** in 39% overall yield from **1**. This epimer of shikimic acid has not been previously synthesized but its methyl ester (6) and a related triacetate **10** are known (7). Hydrolysis of the acetonide **8**, as before, and acetylation confirmed the identity (^{1}Hmr) and stereochemistry of our product.

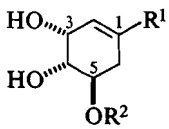
Expoxidations of the double bond similarly timed can produce the other two isomers to shikimic acid. Thus *exo*-epoxides **11** obtained by MCPBA treatment of **1** reacted with LDA at −78°C to afford a 1:1 mixture of two products (86%). These were separated by distillation and identified as epoxycyclohexenol **12** (bp 110°C/0.05 Torr) and cyclopropane **13** (bp 92–100°C/0.05 Torr). The former has recently been con-



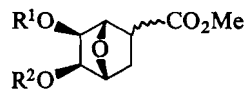
1 (R = CO_2Me)
2 (R = CN)



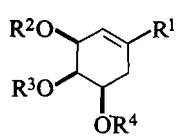
3 (R = CN)
15 (R = CO_2Me)



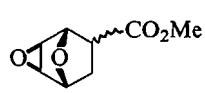
4 (R^1 = CN, R^2 = TBDMS)
5 (R^1 = CO_2H, R^2 = H)



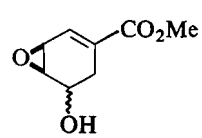
6 (R^1 = R^2 = H)
7 (R^1 + R^2 = CMe_2)



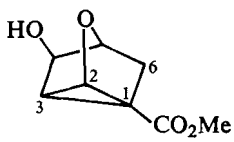
8 (R^1 = CO_2Me, R^2 = R^3 = CMe_2, R^4 = H)
9 (R^1 = CO_2H, R^2 = R^3 = R^4 = H)
10 (R^1 = CO_2Me, R^2 = R^3 = R^4 = Ac)



11



12 (β-OH)
14 (α-OH)



13

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[2] Shikimic acid and related metabolites have recently been the focus of much synthetic interest. For a review, see ref. 4*a*; for later work, see ref. 4*b*.

verted (8) into (±) methyl 4-epishikimate. Epoxidation of the diene **15** (1) with MCPBA and CH_2Cl_2 (73%), followed by desilylation (tetrabutylammonium fluoride), provided a 7:1 mixture (400 MHz ^{1}Hmr) of **14** and **12**. The former has recently been isolated and synthesised (9).[3]

We are proceeding with our experiments to convert **14** into the all-*trans* 3-epishikimic acid and to employ these techniques in the synthesis of other shikimate related metabolites.[4]

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1. B. A. KEAY, D. RAJAPAKSA, and R. RODRIGO. Can. J. Chem. In press.
2. J. E. BALDWIN. J. Chem. Soc. Chem. Commun. 734 (1976); J. E. BALDWIN, J. CUTTING, W. DUPONT, L. KRUSE, L. SILBERMAN, and R. C. THOMAS. J. Chem. Soc. Chem. Commun. 736 (1976).
3. B. A. KEAY and R. RODRIGO. Can. J. Chem. **61**, 637 (1983).
4. (*a*) B. GANEM. Tetrahedron, **34**, 3353 (1978); (*b*) K. E. COBLENS, V. B. MURALIDHARAN and B. GANEM. J. Org. Chem. **47**, 5041 (1982); R. H. SCHLESSINGER and A. LOPES. J. Org. Chem. **46**, 5252 (1981); M. KOREEDA and M. A. CIUFOLINI. J. Am. Chem. Soc. **104**, 2308 (1982); D. A. MCGOWAN and G. A. BERCHTOLD. J. Am. Chem. Soc. **104**, 1153 (1982); B. GANEM. N. IKOTA, V. B. MURALIDHARAN, W. S. WADE, S. D. YOUNG, and Y. YULIMOTO. J. Am. Chem. Soc. **104**, 6787 (1982); G. W. J. FLEET and T. K. M. SHING. J. Chem. Soc. Chem. Commun. 849 (1983).
5. W. L. NELSON, D. R. ALLEN, and F. F. VINCENZI. J. Med. Chem. **14**, 698 (1971); F. KIENZLE. Helv. Chim. Acta, **58**, 1180 (1975); W. G. DAUBEN and H. O. KRABBENHOFT. J. Am. Chem. Soc. **98**, 1992 (1976); F. BRION. Tetrahedron Lett. 5299 (1982).
6. R. GREWE and S. KERSTEN. Chem. Ber., **100**, 2546 (1967).
7. T. ETHERINGTON, R. B. HERBERT, F. G. HOLLIMAN, and J. B. SHERIDAN. J. Chem. Soc. Perkin Trans. 1, 2416 (1979).
8. D. A. MCGOWAN and G. A. BERCHTOLD. J. Am. Chem. Soc. **104**, 7036 (1982).
9. T. FEX, J. TROFAST, and B. WICKBERG. Acta Chem. Scand. Ser. B, **35**, 91 (1981).

[3] We are grateful to a referee for calling our attention to this paper and to ref. 6.

[4] All compounds prepared in this study provided analytical and (or) spectroscopic data consistent with the assigned structures. Full details will be published later.