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TOTAL SYNTHESIS OF PICROTIN

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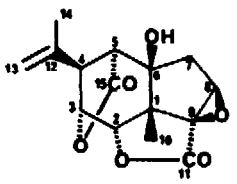
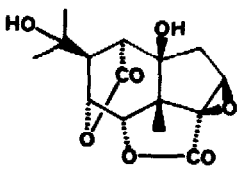
Summary: The conversion of picrotoxinin (1) to picrotin (2), which completes the total synthesis of the latter, is described.

Picrotoxin, first isolated in crystalline form in 1811 as the bioactive principle of Menispermum cocculus,[1,2] consists of an equimolar mixture of two components which can be detected by proton magnetic resonance and separated by chromatography on silica gel, picrotoxinin (1) and picrotin (2). A total synthesis of picrotoxinin



1



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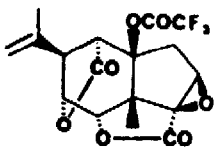

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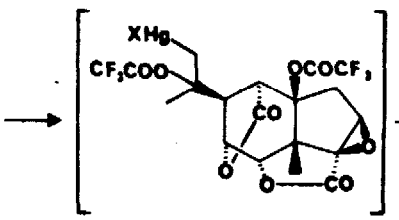

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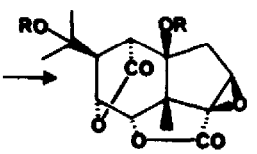

5 R = $COCF_3$

2 R = H

has recently been described.[3] In this note we report on a conversion of picrotoxinin to picrotin which completes a total synthesis of the latter. Although the transformation of 1 to 2 formally requires only Markovnikov hydration of the isopropenyl appendage, this direct approach is obstructed by the strong tendency for participation of the hydroxyl function at C-6 in electrophile induced addition to the

12,13-double bond.[2] Consequently an indirect approach to the conversion 1 → 2 was studied.

Treatment of picrotoxin with 5 equiv of trifluoroacetic anhydride in pyridine containing 1 equiv of 4-dimethylaminopyridine[4] at 45° for 22 hr gave the 6-trifluoroacetoxy derivative 3. Reaction of 3 with mercuric trifluoroacetate in 3:1 benzene-tetrahydrofuran at 23° for 6 hr afforded cleanly the organomercurial 4 (X=Cl) after treatment with 2 equiv of aqueous potassium chloride at 23° for 15 hr and extractive workup.[5] Reaction of 4 with excess tri-n-butyltin hydride in ethanol at 0° gave picrotin bis trifluoroacetate (5) (35%) along with trifluoroacetyl picrotoxinin (3) (60%).[6,7] Treatment of the mixture with excess sodium bicarbonate in aqueous methanol afforded, after chromatography to separate 1, synthetic picrotin (2) identical in all respects with naturally derived material (30% from 1, and 75% corrected for recovered 1).[8]

References and Notes

1. P. F. G. Boullay, Ann. Chim. Phys. (Paris), 80, 209 (1811).
2. For a review see C. J. Coscia, "Cyclopentenoid Terpene Derivatives," W. I. Taylor, A. R. Battersby Eds., Marcel Dekker, New York, 1969, Chapter 2, pp. 147-201.
3. E. J. Corey and H. L. Pearce, J. Am. Chem. Soc., 101, 5841 (1978).
4. G. Höfle, W. Steglich, and H. Vorbrüggen, Angew. Chem. Int. Ed. Eng., 17, 569 (1978).
5. H. B. Henbest and B. Nicholls, J. Chem. Soc., 227 (1959).
6. G. M. Whitesides and J. San Filippo, J. Am. Chem. Soc., 92, 661 (1970).
7. It should be mentioned that the more conventional reagent for replacement of mercury by hydrogen, sodium borohydride, effected clean elimination to form 3 rather than the desired 5. An attempt to effect the transformation of 4 to 2 by bicarbonate promoted cleavage of trifluoroacetyl groups followed by hydride reduction was unsuccessful. Our results suggest the need for new procedures and/or reagents for the displacement of mercury by hydrogen particularly with β-substituents such as trifluoroacetoxy.

8. This investigation was assisted financially by a grant from the National Science Foundation.

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