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# A NEW EXPEDITIOUS SYNTHESIS OF (+)-EXO-BREVICOMIN VIA EFFICIENT C-C BOND FORMATION OF TRIFLATES

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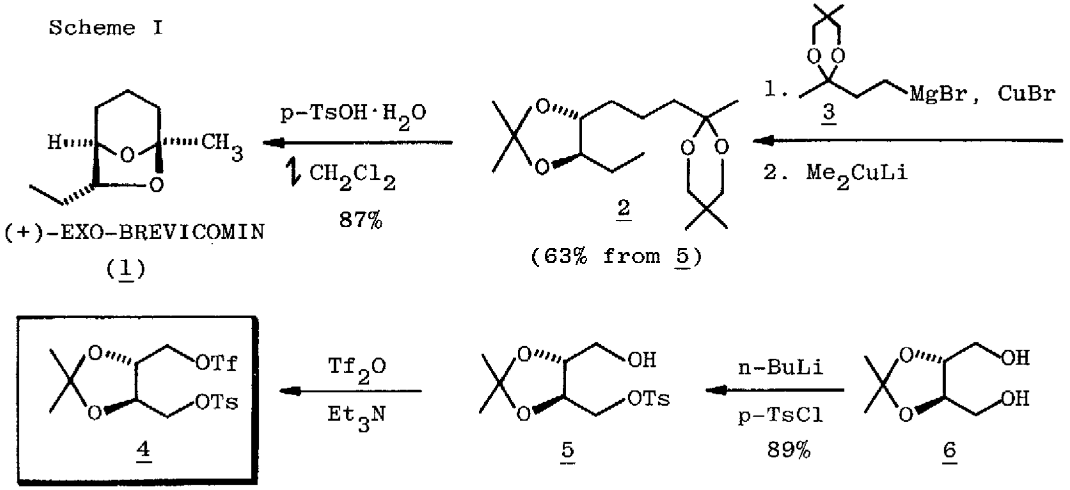
Abstract: A new expeditious synthesis of (+)-exo-brevicomin from diethyl D-tartrate as a chiral source is accomplished via an efficient carbon-carbon bond forming reaction of triflates as a key step.

Recently, we have reported a new powerful carbon-carbon bond forming reaction at the carbon center bearing a β-oxygen functionality.[1] The method relies on a copper(I)-catalyzed Grignard reaction with reactive triflates. Within the paper we have also mentioned that the procedure provides a *convenient methodology of preparing chiral compounds from simple chiral* building blocks. To realize this concept a new expeditious synthesis of (+)-exo-brevicomin (1), one of the aggregation pheromones of bark beetles,[2] has been carried out by using diethyl D-tartrate as a chiral source. Although there are several reports on the synthesis of this target molecule, it still remains a considerable synthetic challenge to devise a highly successful strategy.[3]

As shown in antithetic form in Scheme I, in our improved synthesis the direct preparation of ketal-acetonide 2[4] from tosyl-triflate 4 is the most important step. The unprecedented structure of 4 as a key intermediate has facilitated the control of the reactivity of two hydroxyl functions, and hence a new selective procedure to introduce the two kinds of nucleophiles has been established.

Treatment of diol 6, which is readily available from diethyl D-tartrate,[5] with n-BuLi followed by p-TsCl provided monotosylate 5, $[\alpha]^{21}_D$ +11.3°(c 2.70, $CHCl_3$)[lit.[5] -12.2°for the enantiomer], in 89% yield.[6] Then 5 was converted into tosyl-triflate 4, $[\alpha]^{21}_D$ +7.6°(c 1.26, $CHCl_3$), with triflic anhydride in the presence of triethylamine. One-pot procedure for performing the double alkylation of 4 was accomplished first by the action of 1.05 equiv. of the Grignard reagent (3)[7] in the presence of 0.2 equiv. of CuBr (0 °C, 4 h) and second by introduction of 3 equiv. of $Me_2CuLi$ (room temperature, 10 h).[8] By this sequence the desired product 2, $[\alpha]^{17}_D$ +16.8° (c 0.80, $CHCl_3$), was obtained in 63% yield from 5. The last step of intramolecular transketalization of 2 was proceeded simply by refluxing in

Scheme I



dichloromethane with a catalytic amount of p-toluenesulfonic acid to afford (+)-exo-brevicomin (1), $[\alpha]^{21}_{D}$ +67.7°(c 1.0, $Et_2O$) [lit.[9] +84.1°], in 87% yield. The overall yield of 1 for four operations from 2 was 48.8%! This result clearly demonstrates that the present study constitutes the best synthetic route to reach the title compound.[3]

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## References and Notes

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2. R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, and L. E. Browne, Science, 159, 889(1968).
3. For the most recent works, see B. Giese and R. Rupaner, Synthesis, 1988, 219; J. S. Yadav, P. S. Reddy, and B. V. Joshi, Tetrahedron, 23, 7243 (1988), and references cited therein. Among previous examples, to the best of our knowledge, the most efficient synthesis is recorded by Masaki et al.: six-step sequence from diethyl D-tartrate in 32.3% overall yield. See Y. Masaki, K. Nagata, Y. Serizawa, and K. Kaji, Tetrahedron Lett., 23, 5553(1982).
4. We have also succeeded to prepare 2 via a stepwise method from 6. Full details will be reported elsewhere.
5. For a general review, see D. Seebach in "Modern Synthetic Methods," Vol. 2, R. Scheffold, Ed., Verlag Sauerlaender, 1980, pp 115-171.
6. The reported procedure (p-TsCl, pyridine) to obtain monotosylate 5 is less satisfactory (61% yield). See ref. 5.
7. J. C. Stowel, D. R. Keith, and B. T. King, Org. Syn., 62, 140(1983).
8. The reverse addition of these reagents was fruitless due to the higher reactivity of $Me_2CuLi$.
9. K. Mori, Tetrahedron, 30, 4223(1974).

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