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AN EFFICIENT METHOD FOR THE ALKYLATION OF CHIRAL TRIFLATES WITH ALKYNYLLITHIUM REAGENTS. A HIGHLY CONCISE TOTAL SYNTHESIS OF (+)-PANAXACOL[1]

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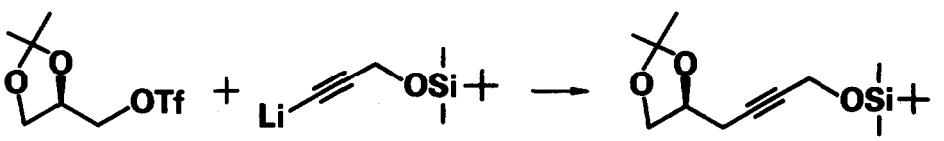
Abstract: An efficient method for the alkylation of triflates with alkynyllithium reagents is described and the successful application of the method to the total synthesis of (+)-panaxacol is exemplified.

Recently, we reported an efficient method for carbon-carbon bond formation at the carbon center bearing β-oxygen functions via trifluoromethanesulfonate (triflate) derivatives.[2] In the course of our studies to explore the synthetic utility of this technology in natural product synthesis, we found that the triflates are indeed very reactive substrates for the alkylation with acetylenic nucleophiles.

As previously noted in the literature,[3] the coupling reaction of alkynyllithium reagents on tosylates or iodides bearing β-oxygen functions does not proceed very well. However, Carling and Holmes have recently shown that the corresponding triflates can act as a reactive substrate.[4] Apart from this preliminary study, there are no reports of the general use of this type of transformation in natural product synthesis.

Our initial investigations (Scheme 1) revealed that the reaction of **1** with **2** in THF gave the desired coupling product **3**, but the reaction was

Scheme 1

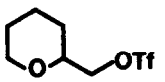
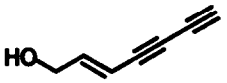
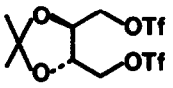
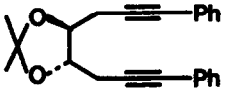
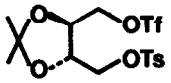
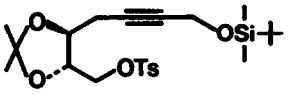
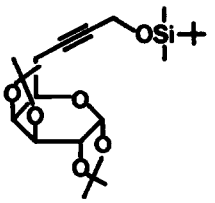


1 **2** **3**

Solvent	Reaction conditions	Yield, %
THF-DMPU (6 : 1)	-20 °C, 10 min	87
THF-HMPA (6 : 1)	-20 °C, 10 min	76
THF only	rt, 14 h	60

slow and the yield was only 60%. After the examination of various reaction conditions to improve the product yield, the mixed solvent system employing THF-dimethylpropyleneurea (DMPU)[5] (6:1 ratio) was found to be the best: the reaction proceeded cleanly at -20 °C within 10 min to afford **3** in 87% yield (Scheme 1).[6] Some other successful results are shown in the Table.

Table. Coupling Reactions of Triflates with Alkynyllithium Reagents[a]

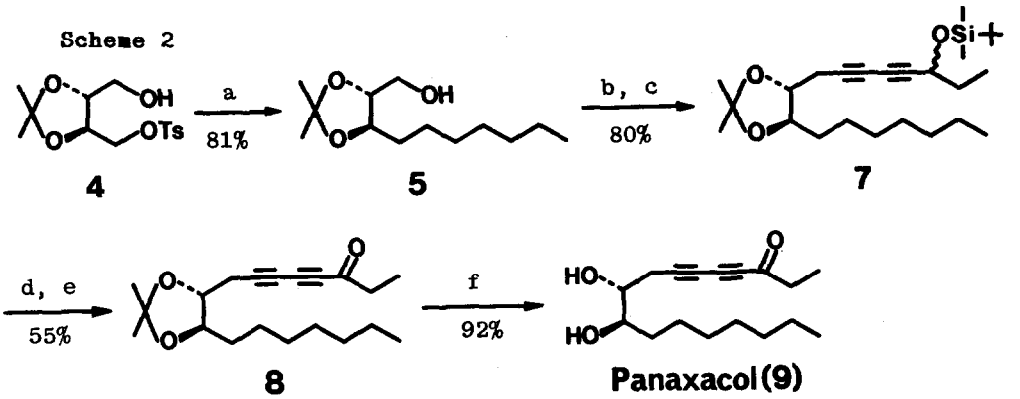
Entry	Substrate	Li—≡—R[b]	Reaction conditions	Product	Yield, %[c]
1		**2**	-78 °C, 2 h		87
2	**1**	Li—≡—C_6H_{13}	-20 °C, 15 min		57
3	**1**	Li—≡—≡—TMS[d]	-20 °C, 30 min		48
4		Li—≡—Ph	-20 °C, 10 min		55
5		**2**	-20 °C, 5 min		88
6		**2**	0 °C, 6.5 h		62

[a] All reactions were performed in THF-DMPU (6:1).
[b] Unless otherwise noted the reagent was prepared from the starting alkyne derivatives by treatment with 1.0 equiv. of n-BuLi at 0 °C.
[c] Overall yield of chromatographed pure product from the starting alcohol.
[d] Prepared from 1,4-bis(trimethylsilyl)-1,3-butadiyne by treatment with 1.0 equiv. of MeLi: see ref 7.

The Table reveals that the present method is effective in introducing the alkyne unit into the carbon center bearing β-oxygen functions. In addition, the chemoselectivity was observed (Entry 5) when the exclusive substitution on the triflate occurred. In a case (Entry 3) only an ene-diyne compound, formed by β-elimination[8] of the initial coupling product and deprotection of trimethylsilyl group,[9] was isolated after the conventional aqueous treatment.

In order to demonstrate the utility of this reaction we performed the short-step synthesis of panaxacol (9) (Scheme 2), an anticancer compound isolated from the callus of *Panax gingeng*.[10]

Scheme 2



(a) $(C_6H_{13})_2CuLi$, THF-Me_2S, -15 °C, 1.5 h; (b) Tf_2O, Et_3N, CH_2Cl_2, -15 °C, 15 min; (c) $HC{\equiv}C{-}C{\equiv}C{-}CH(OSiMe_2Bu^t)CH_2CH_3$ (**6**), n-BuLi, THF-DMPU, -20 °C, 30 min; (d) n-Bu_4NF, THF, rt, 30 min; (e) $(COCl)_2$, DMSO, THF, -78 °C, 1 h, then Et_3N, -78 °C →rt, 1 h; (f) 2N HCl, MeOH, rt, 22 h.

The introduction of hexyl group on the monotosylate **4**[2a] was achieved conveniently by the action of 6 equiv. of $(C_6H_{13})_2CuLi$ in THF-Me_2S (1:1) to give the alcohol **5** in 81% yield. Triflation followed by reaction with 1.5 equiv. of **6**[11] in THF-DMPU (6:1) gave cleanly **7** as a diastereomeric mixture in 80% yield. After removal of the silyl group, Swern oxidation afforded the ketone **8** in 55% yield. Finally, acid hydrolysis of **8** provided (+)-panaxacol (**9**) in 92% yield. A comparison of its specific rotation ($[\alpha]^{18}_D$ +21.3°(c 0.76, MeOH)) with literature data ($[\alpha]^{22}_D$ +19.5° (c 1.0, MeOH))[10a] confirmed its correct absolute configuration. The spectral data (IR, ^1H and ^{13}C NMR) were in good agreement with those of an authentic sample kindly provided by Prof. Fujimoto. Thus, readily available chiral compound **4** was efficiently converted to panaxacol (**9**) through a simple six-step sequence in 32.8% overall yield.

In conclusion, the results presented here clearly illustrate the usefulness of chiral triflate methodology. Further work for applying this method to the other biologically interesting natural products is currently under investigation.

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References and Notes

1. A part of this work was presented at the 17th International Symposium on the Chemistry of Natural Products (IUPAC), New Delhi, India, February 4-9, 1990 (Abstract OC 21).
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5. D. Seebach, *Chem. Br.*, **1985**, 632.
6. At -78 °C the reaction was very slow and less effective.
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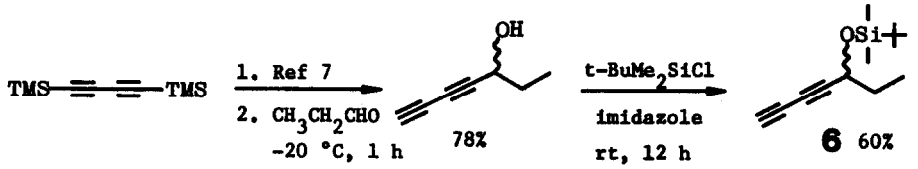
8. The ease of the similar type of β-elimination in the presence of HMPA has been reported: E. J. Corey and C. Rücker, *Tetrahedron Lett.*, **23**, 719 (1982).
9. The concomitant hydrolysis of trimethylsilyl group seems to be caused by the aqueous workup, since it has been known that this kind of trimethylsilyl group is rapidly hydrolyzed under the basic conditions: H. Gilman, A. G. Brook, and L. S. Miller, *J. Am. Chem. Soc.*, **75**, 4531 (1953). See also: W. P. Weber, "Silicon Reagents for Organic Synthesis," Springer-Verlag, Berlin, 1983; Chap. 9-4.
10. (a) Y. Fujimoto and M. Satoh, *Phytochemistry*, **26**, 2850 (1987). (b) Idem, *Chem. Pharm. Bull.*, **36**, 4206 (1988). (c) Y. Fujimoto, M. Satoh, N. Takeuchi, and M. Kirisawa, *Chem. Lett.*, **1989**, 1619. The first enantiospecific total synthesis of panaxacol was accomplished by Prof. Fujimoto, et al. and its absolute configuration was established: see ref 10c.
11. The alkynyl reagent **6** was prepared as follows:



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