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STEREOSELECTIVE SYNTHESIS OF TRISUBSTITUTED OLEFINS

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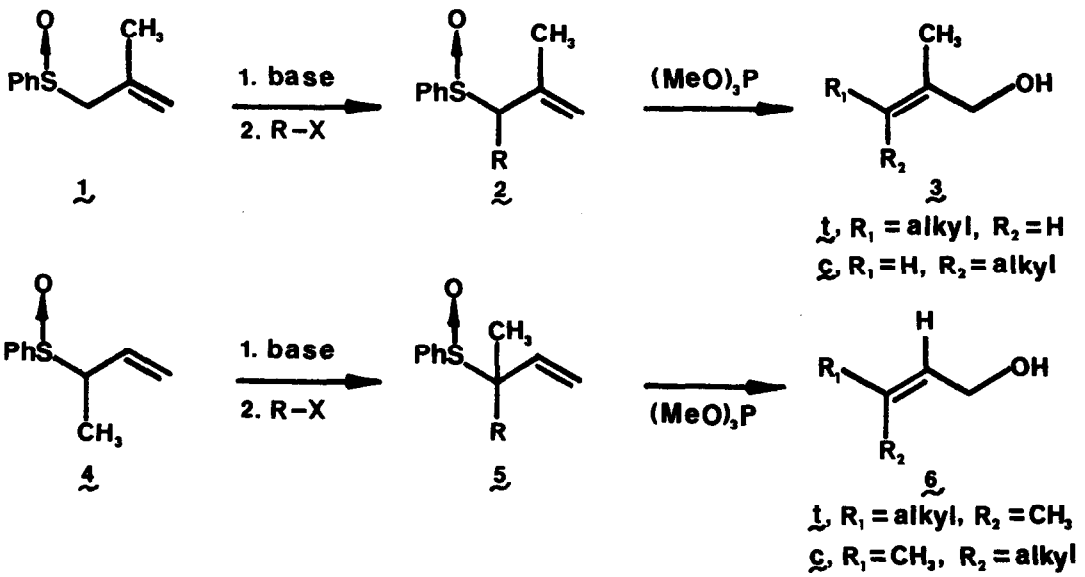
In the preceeding communication the application of allylic sulfoxides to a general synthesis of allylic alcohols was described.[2] The purpose of this disclosure is to demonstrate the applicability of sulfoxide-stabilized allylic carbanions to the synthesis of trisubstituted olefinic allylic alcohols.

The two general olefin trisubstitution patterns of interest in this study were of the type 3t and 6t, both of which are common structural components in polyisoprenoid substances.[3] For both practical and theoretical considerations we were particularly interested in the effects of allyl substitution on olefin geometries resulting from [2,3] sigmatropic rearrangement and subsequent cleavage[4] of sulfoxides 2 and 5. To answer these questions, the sulfoxide-stabilized allylic carbanions derived from 1 and 4[5] were treated with a variety of alkyl and allylic

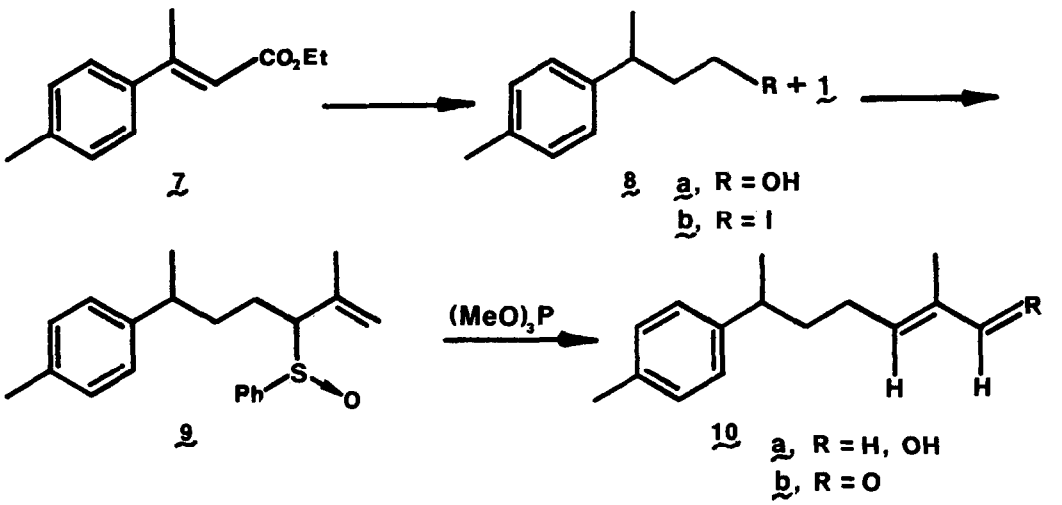


t, R_1 = alkyl, R_2 = H
c, R_1 = H, R_2 = alkyl

t, R_1 = alkyl, R_2 = CH_3
c, R_1 = CH_3, R_2 = alkyl

halides affording the α-alkylated derivatives 2 and 5 in addition to the products derived from γ-alkylation (cf. Table for α:γ ratios).[6] The resulting sulfoxides were transformed in situ with trimethyl phosphite-methanol into the allylic alcohols 3t, 3c and 6t, 6c respectively. As summarized in the Table, the alkylation of 1 and 4 with a variety of alkyl halides followed by rearrangement of the resulting sulfoxides 2 and 5 affords in all cases a predominance of the trans-trisubstituted olefins 3t and 6t.[7]

Scheme I

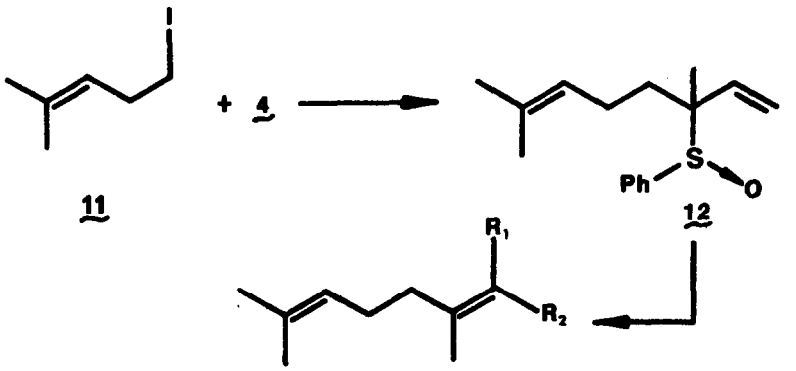


7 8 a, R = OH; b, R = I 9 10 a, R = H, OH; b, R = O

Application of this olefin sequence to the synthesis of the sesquiterpene nuciferal (10b)[3a] is illustrated in Scheme I. The cinnamate ester 7,[8] prepared from p-methylacetophenone and trimethylphosphonoacetate in 64% yield,[9] was smoothly reduced to the alcohol 8a with $LiAlH_4$ in THF (45°, 2 hr) in 90% yield (bp 110°, 1 mm Hg). Conversion of 8a to the iodide 8b was accomplished routinely with methyl iodide-triphenyl phosphite.[10] Alkylation of the allylic anion derived from 1 with 8b afforded 9 as well as some γ-alkylated material (α:γ = 2). Cleavage of 9 with trimethyl phosphite-methanol yielded the trans-allylic alcohol 10a in 43% yield uncontaminated by the cis-isomer as evidenced by nmr analysis.[11,12] Manganese dioxide oxidation of 10a afforded (±) nuciferal (10b) in 99% yield.[13] Alkylation of 1 with other alkyl and allylic halides and subsequent cleavage to the allylic alcohols[5] 3t, 3c afforded the trans-isomers in greater than 95% isomeric purity. The results of our study on the alkylation of 1 and subsequent rearrangement to 3t, 3c are not in complete accord with those reported by Grieco.[15]

To gain information on the relative proportion of cis and trans-allylic alcohols derived from the rearrangement of allylic sulfoxides of the general type 5, the synthesis of geraniol 13t and nerol 13c outlined in Scheme II was carried out. Alkylation of the anion derived from 4 with 11[16] afforded the α-alkylated product 12 as well as the γ-isomer (α:γ = 2.3). In situ cleavage of 12 at room temperature resulted in a 90:10 ratio of geraniol 13t and nerol 13c in 55% yield. The relatively high degree of selectivity observed in the rearrangement of 12 is

Scheme II



13 t, $R_1 = H$, $R_2 = CH_2OH$
c, $R_1 = CH_2OH$, $R_2 = H$

surprising in view of other published work on [2,3] sigmatropic rearrangements leading to olefins having a similar substitution pattern.[17] At this time the intimate details that govern the allylic olefin geometry are unknown since the relative rates of the rearrangement and cleavage steps have not been determined.

Table. Alkylation-Rearrangement of Allylic Sulfoxides

Sulfoxide	R-X	Alkylation[a] Conditions	α:γ[b] Ratio	ROH, Yield%[c]	%trans:[d] %cis
1	CH_3I	-50°, 10 min	10	(75)	97:3
1	$n\text{-}C_6H_{13}I$	-30°, 2 hr	2.5	3t,3c 42	96:4
1	$(CH_3)_2C{=}CHCH_2Br$	-30°, 2 hr	2.0	46	96:4
1	8b	-20°, 6 hr	2.0	10a 43	>95:<5[e]
4	CH_3I	-60°, 20 min	2.6	59	---
4	C_2H_5I	-50°, 5 hr	2.4	6t,6c (48)	73:27
4	$(CH_3)_2C{=}CCH_2Br$	-40°, 2 hr	1.1	35	93:7
4	11	-8°, 10 min[f]	2.3	13t,13c 55(70)	90:10

a Carried out according to the procedure described in ref. 2. b Products derived from α-alkylation were isolated and characterized. The α:γ-ratios were determined either by nmr or isolation. c Figures in parenthesis refer to glc or nmr yields relative to an internal standard; other figures refer to isolated yields based on sulfoxide 1 or 4. d Determined by glc by comparison with authentic samples of cis and trans-isomers.[14] e No cis-isomer as evidenced by nmr analysis. f The halide was added to the anion at -30° and the temp was raised to -8°.

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References

1. Camille and Henry Dreyfus Teacher-Scholar recipient, A. P. Sloan Fellow, 1972-1974.
2. D. A. Evans, G. C. Andrews, T. T. Fujimoto, D. Wells, Tetrahedron Lett., 0000, (1972).
3. For examples of terpenes containing the 3t substructural unit see: (a) T. Sakai, K. Nishimura, Y. Hirose, Bull. Chem. Soc. Japan, 38, 381 (1965); (b) G. Brieger, Tetrahedron Lett., 2123 (1963); (c) R. A. Flath, R. E. Lundin, R. Teranishi, ibid., 295 (1966); (d) W. H. Nutting, H. Rapoport, L. Machlis, J. Amer. Chem. Soc., 90, 6434 (1968).
4. D. A. Evans, G. C. Andrews, ibid., 94, 3672 (1972).
5. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, ibid., 90, 4869 (1968).
6. The alkylation and sulfoxide cleavage conditions used in this study were those reported in the preceeding communication, ref 2.
7. Satisfactory spectra and elemental analyses have been obtained for all new compounds reported herein.
8. M. A. Psarrea, C. Sandris, G. Tsatsas, Bull Soc. Chim. France, 2145 (1961).
9. W. S. Wadsworth, Jr., W. D. Emmons, J. Amer. Chem. Soc., 83, 1733 (1960).
10. S. R. Landauer, H. N. Rydon, J. Chem. Soc., 2224 (1953).
11. The cis-isomer is a naturally occurring compound whose nmr spectrum has been published, ref 3a.
12. For the determination of trisubstituted olefin geometries of this type see: U. T. Bhalerao, H. Rapoport, J. Amer. Chem. Soc., 93, 4835 (1971); H. C. Kretschmar, W. F. Erman, Tetrahedron Lett., 41, (1970); K. C. Chan, R. A. Jewell, W. H. Nutting, H. Rapoport, J. Org. Chem., 33, 3382 (1968).
13. The ir, nmr and mass spectra of 10b are identical to those published for nuciferal, ref 3a.
14. Authentic samples of the cis-isomers 3c (R=C_6H_{13}, CH_3) were prepared by Corey's procedure: E. J. Corey, H. Yamamoto, J. Amer. Chem. Soc., 92, 226 (1970).
15. P. A. Grieco, Chem. Commun., 702 (1972). This worker reports no γ-alkylation; we have found this side reaction unavoidable under his reaction conditions. Also, the reported use of n-butyllithium leads to lower yields, ref 2.
16. Prepared by a modification of Julia's procedure where HI was substituted for HBr. M. Julia, S. Julia, R. Guegan, Bull Soc. Chim. France., 1072 (1960).
17. V. Rautenstrauch, Helv. Chim. Acta, 54, 739 (1971); J. E. Baldwin, J. DeBernardis, J. E. Patrick, Tetrahedron Lett., 353 (1970).