

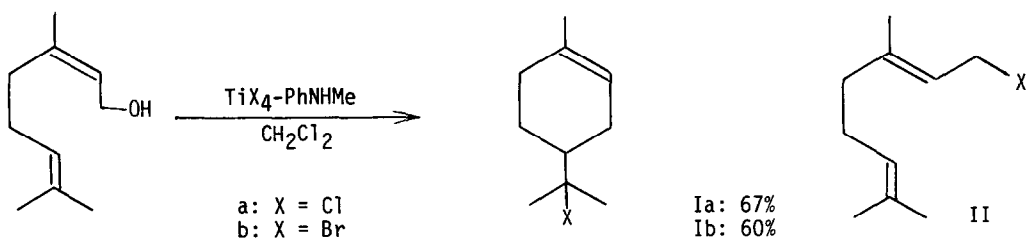
INTRAMOLECULAR CYCLIZATION OF NEROL AND THE RELATED (Z)-ALLYLIC ALCOHOLS
BY MEANS OF $TiCl_4$ -PhNHMe COMPLEX. SYNTHESIS OF NEZUKONE

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Abstract: Nerol is cyclized to terpinyl chloride or bromide in the presence of TiX_4 -PhNHMe (1:1) complex in dichloromethane at $-23^\circ C$, while cyclization of (Z)-allylic alcohols $CH_2=CR-CH_2CH_2CMe=CHCH_2OH$ (R = H, Me, Cl) produces seven-membered ring products in fair yields.

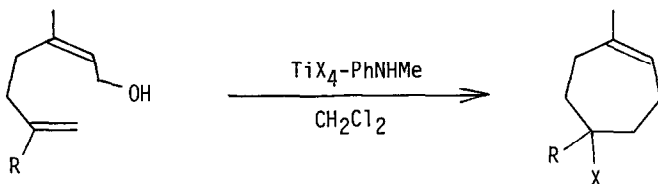
The previously reported reaction of diethyl neryl phosphate with organoaluminum reagents of the type R_2AlX (X = OR, NHR etc.) has led to the stereospecific synthesis of limonene and similar cyclic terpenes.¹ We wish to report a further development of this type of cyclization technique which is more efficient and much simpler.

Addition of N-methylaniline (1.5 mmol) to a solution of TiX_4 (X = Cl or Br, 1.5 mmol) in dichloromethane at $0^\circ C$ gave a complex.² Both the chloride and the bromide reacted smoothly at $-23^\circ C$ with nerol itself (1.0 mmol) providing terpinyl halides Ia and Ib,³ respectively, in fair yields. In contrast to the previous organoaluminum reactions, terpinyl cation is thus stabilized by halide ion-uptake rather than by proton-loss. Analogous treatment of geraniol with each of the above complexes produced the respective geranyl halide⁴ II quantitatively.



Reaction of nerol with $TiCl_4$ alone afforded a complex mixture which did not contain Ia. Apparently the presence of the amine was essential. A complex $TiCl_4$ -2,2,6,6-tetramethylpiperidine gave Ia in 65% yield, and VCl_4 -PhNHMe (50%) and $AlCl_3$ -PhNHMe (38%) were found to be marginal.⁵ Meanwhile, such halides as $ZrCl_4$, WCl_6 and $SnCl_4$ gave no sign of cyclized products with or without an amine.

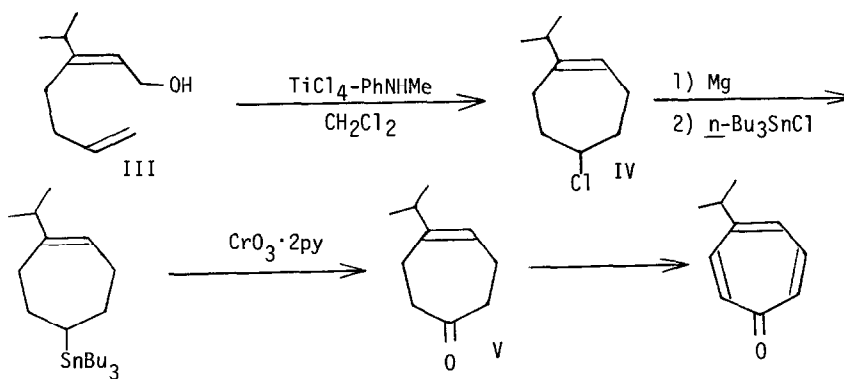
Treatment of (Z)-allylic alcohols $CH_2=CR-CH_2CH_2-C(CH_3)=CHCH_2OH$ (R = H, CH_3 , Cl)⁶ with the complex TiX_4 -PhNHMe produced seven-membered ring products carrying X on the R-substituted carbon. The yields in Table I are satisfactory and this provides a novel route to cycloheptenes, whereas the (E)-isomers gave the corresponding allylic halides⁴ similarly to the geraniol case.

Table I: Seven-membered ring formation by means of TiX_4 -PhNHMe complexes


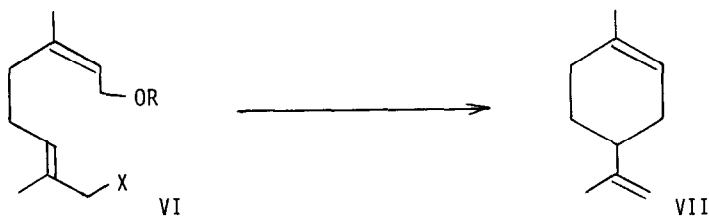
R	X	Y(%)
H	Cl	65
H	Br	56
Me	Cl	66
Cl	Cl	18 ^a

a. The corresponding allylic chloride was obtained in a 54% yield.

The present method has provided us with a simple route to troponoid derivatives, which has been exemplified by the synthesis of nezukone. The transformation of allylic alcohol III⁸ to cycloheptenyl chloride IV⁹ was easily performed in 60% yield by means of $TiCl_4$ -PhNHMe complex. None of the conceivable S_N2 type reactions worked at all with the C-Cl bond of IV, which was always recovered unchanged.¹⁰ This difficulty was solved by trapping the Grignard reagent derived from IV with Bu_3SnCl and successive oxidation by the Still's method¹¹ providing cycloheptenone V¹² (65%). Nezukone was obtained by simple bromination-debromination procedure (60%).^{13,14}



Finally, an extremely selective synthesis of limonene has been achieved.^{15,16} Treatment of VIa¹⁷ and VIc¹⁸ with $TiCl_4$ -PhNHMe complex has given limonene exclusively in good yields. The new method is superior to the previously reported one using organoaluminum reagent^{1d} as far as the cyclization yield and selectivity are concerned.¹⁹

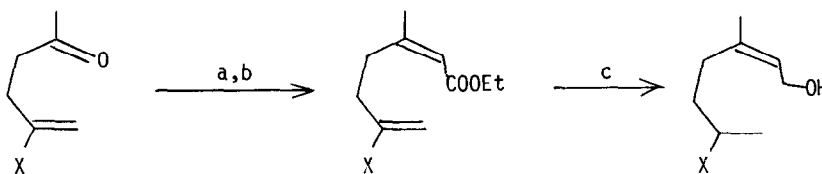


	X	R	Reagent	Yield of VII(%)
VIa	SiMe ₃	H	TiCl ₄ -PhNHMe/CH ₂ Cl ₂	79
VIb	SiMe ₃	COCH ₃	MeAl(OCOCF ₃) ₂ /hexane	29 ^a
VIc	SnBu ₃	H	TiCl ₄ -PhNHMe/CH ₂ Cl ₂	73
VIId	SnBu ₃	COCH ₃	MeAl(OCOCF ₃) ₂ /hexane	51

a. The polymeric products were obtained.

References and Notes

- (a) Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **98**, 5030 (1976). (b) S. Hashimoto, Y. Kitagawa, S. Iemura, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 2615 (1976). (c) S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 4192 (1977). (d) H. Yamamoto and H. Nozaki, *Angew. Chem. Internat. Ed. Engl.*, **17**, 169 (1978).
- V. H. Burger and H. J. Neese, *Z. Anorg. Allg. Chem.*, **365**, 243 (1969).
- The halides Ia and Ib are slowly decomposed on treatment with silica gel in dichloromethane at room temperature to produce a complex mixture of hydrocarbons mainly consisting of limonene and terpinolene. Analytical samples were obtained by column chromatography on silica gel. The column was cooled with Dry-Ice.
- The TiCl₄-PhNHMe complex, therefore, provides an efficient method for the transformation of allylic alcohol to allylic halides. Previous methods: (a) G. Stork, G. Calzada and J. Hooz, *Tetrahedron Lett.*, 1393 (1969), (b) G. Stork, P. A. Grieco, and M. Gregson, *Org. Syn.*, **54**, 63, 68 (1974) and (c) E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Lett.*, 4339 (1972).
- In an attempt to find the suitable amine, we studied the reaction of nerol with a variety of amines and TiCl₄. The yields of resulting terpinyl chloride (amine) are given: 67% (PhNHMe); 65% (2,2,6,6-tetramethylpiperidine); 32% (Et₂NH); 28% (α -phenethylamine); 40% (DABCO); 52% (Et₃N); none (pyridine).
- The allylic alcohols were prepared by the following scheme:



- (a) $\text{Me}_3\text{SiCHLiCOOEt}$ (ref. 7), (b) E, Z separation by chromatography on silica gel, and (c) AlH_3 reduction.
7. K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 1620 (1974).
 8. Prepared from 2-methyl-6-hepten-3-one, which was derived from isopropyl methyl ketone -dimethylhydrazone and allyl bromide (E. J. Corey and D. Enders, *Tetrahedron Lett.*, **3** (1976)) by the similar sequences as ref. 6.
 9. The details of the seven membered ring synthesis are illustrated by the procedure for the transformation of III to IV. To a solution of TiCl_4 -PhNHMe complex derived from TiCl_4 (1.0 M solution in CH_2Cl_2 , 3.0 ml, 3.0 mmol) and PhNHMe (0.32 g, 3.0 mmol) at 0 °C in CH_2Cl_2 (15 ml) was added a solution of III (0.31 g, 2.0 mmol) in CH_2Cl_2 (3.0 ml) at -23 °C, and the resulting suspension was held there for 30 min. The mixture was diluted with ether (20 ml) and washed with 1N hydrochloric acid and brine. Purification by column chromatography on silica gel with ether-hexane (1:5) afforded the cyclized chloride IV (0.21 g, 60%) as a colorless oil: NMR(CCl_4): δ 0.93 (d, $J = 7$ Hz, 6H), 1.5-2.6 (m, 9H), 4.10 (m, 1H), 5.53 (t, $J = 5$ Hz, 1H); elemental analysis Found: C, 69.8; H, 9.70% (calcd for $\text{C}_{10}\text{H}_{17}\text{Cl}$: C, 69.6; H, 9.92%).
 10. The failure of all the $\text{S}_{\text{N}}2$ type reactions attempted is ascribed to the opposed π bond. See S. J. Rhoads, J. M. Watson, and J. G. Kambouris, *J. Am. Chem. Soc.*, **100**, 5151 (1978).
 11. W. C. Still, *ibid.*, **99**, 4836 (1977).
 12. IR(neat) 1705 cm^{-1} (C=O); NMR(CCl_4): δ 1.00 (d, $J = 7$ Hz, 6H), 2.0-2.6 (m, 9H), 5.57 (t, $J = 5$ Hz, 1H); exact mass spectrum m/e 152.1189 (calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ 152.1200).
 13. H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1778 (1978).
 14. The obtained compound was spectrometrically identical with natural nezukone.
 15. Another solution of this problem in the termination of the cationic cyclization had been provided by the use of bulky O-base in the R_2AlOAr system. See ref. 1d.
 16. (a) Allylsilanes for termination: I. Fleming and A. Pearce, *J. C. S. Chem. Comm.*, 182 (1976); T. K. Sarkar and N. H. Anderson, *Tetrahedron Lett.*, 3513 (1978). (b) Silyl-acetylenes: K. Utimoto, M. Tanaka, M. Kitai, and H. Nozaki, *ibid.*, 2301 (1978); W. S. Johnson, T. M. Yarnell, R. F. Myers, and D. R. Morton, *ibid.*, 2549 (1978), (c) Silyl enol ethers: See ref. 1c.
 17. Prepared from neryl acetate by the following sequence of the reactions: (1) allylic oxidation, with SeO_2/EtOH , (2) $\text{PBr}_3/\text{ether}$, (3) $\text{PhSnMe}_2/\text{MeOH}$, (4) selective silylation with sec-BuLi (2 equiv) and SiMe_3Cl , (5) Desulfurization with Li/EtNH_2 .
 18. Prepared from neryl acetate as follows: (1) SeO_2/EtOH , (2) PBr_3 , (3) $n\text{-Bu}_3\text{SnLi}$.
 19. Financial support by the Ministry of Education, Science, and Culture, Japanese Government, (Grant-in-Aid #303023 and #375472) is acknowledged.

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