Self-Immolative Asymmetric Synthesis. III. Allylic Rearrangement of Optically Active Trichloroacetimidate

Yukio YAMAMOTO, Hiroshi SHIMODA,* Jun'ichi ODA, and Yuzo INOUYE

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611
**Research Laboratory, Fumakilla Co. Ltd., Ohno-cho, Hiroshima 739-04*

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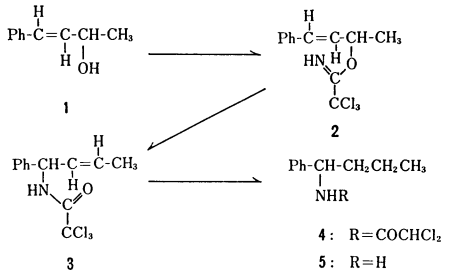
The [3,3]sigmatropic rearrangement of (2*E*)-(1*R*)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate to give *N*-[(2*E*)-(1*R*)-1-phenyl-2-butenyl]trichloroacetamide was effected thermally with nearly complete transfer of chirality *via* a doubly suprafacial transition state. The application of the self-immolative asymmetric synthesis to optically active carveols afforded carveylamines of the predicted configuration.

In the previous papers, we reported transfer of chirality from tetracoordinate nitrogen to trigonal carbon[1] and from tetrahedral carbon to trigonal carbon[2] with nearly quantitative conservation of chirality. These findings not only indicate that the reaction proceeds *via* [2,3]sigmatropic rearrangement but also offer a novel method for stereo-specific synthesis of alcohols from amine oxides with allylic inversion. The reverse transformation, allylic alcohols to amines with allylic inversion, can be achieved by the Chapman-type rearrangements,[3] which are classified as [3,3]sigmatropic rearrangement according to the Woodward-Hoffmann rule. The conversion of an allylic phenylurethane into an *N*-phenylallylamine by Hill was the sole precedent in which the stereochemistry was thoroughly elucidated.[4] In spite of the reasonable stereochemical outcome in favor of a doubly suprafacial mode, the optical yield obtained (65%) was rather moderate in view of the general observations in this type of rearrangements.[5] This may presumably be due to the radical by-path. Recently, the rearrangement of allylic trichloroacetimidates to trichloroacetamides was reported by Overman.[6] This process would be advantageous in enabling one to ensure high yields of primary amines over those which are limited by substituents on nitrogen.

We now present another self-immolative asymmetric synthesis of amines from chiral allylic alcohols by the use of trichloroacetimidic ester as an intermediary. The substrate used in the present study was the chiral trichloroacetimidate, (*E*)-(+)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate [(+)-2].

By the treatment with sodium hydride and trichloroacetonitrile, (*E*)-(+)-4-phenyl-3-buten-2-ol [(+)-**1**, $[\alpha]_D^{20}$ 17.3°][7a,b] was converted to (+)-**2** having $[\alpha]_D^{20}$ 34.7° in 94% yield, whose purity proved to be 85% as assessed by NMR. The trichloroacetimidate (+)-**2** was heated in toluene under reflux to give the [3,3] shift product, (+)-*N*-[(*E*)-1-phenyl-2-butenyl]trichloroacetamide [(+)-**3**, $[\alpha]_D^{20}$ 15.1°] in 74% yield. The *E*-geometry of double bond in resulting (+)-**3** was established by IR and NMR spectra. Neither *Z*-isomer nor [1,3] shift product was detected in the reaction mixture. Hydrogenation of (+)-**3** over palladium charcoal resulted in the formation of the saturated dichloroacetamide [(+)-**4**, $[\alpha]_D^{20}$ 32.7°], one of the 3 chlorine atoms having been simultaneously replaced by hydrogen during the reaction process.



Scheme 1.

The absolute configuration as well as the enantiomeric purity of **4**, crucial to the mechanistic picture of the present rearrangement, were obtained by the conversion of optically pure (−)-1-phenyl-1-aminobutane [(−)-**5**, $[\alpha]_D^{25}$ −22.2°] of the well-defined *S*-configuration[8] into (−)-**4**, $[\alpha]_D^{25}$ −71.7°. Consequently, the end product (+)-**4** and the parent rearrangement product (+)-**3** can be safely assigned the *R*-configuration and should be of 45.6% optical purity.

Since the *R*-configuration of the starting (+)-**1** has been unambiguously established by the correlation to (*R*)-(−)-4-phenyl-2-butanol,[7a,c] and the NMR spectroscopy with the use of a chiral shift reagent showed the chiral alcohol (+)-**1** to be of 45±2% enantiomeric purity, the present thermal rearrangement proceeded with complete retention of chirality.

The finding that the complete transfer of chirality was achieved during the [3,3] shift and that the [1,3] shift product was not detected at all corroborates the concertedness of the process and excludes radical dissociation-recombination. Two transition states would be conceivable for doubly suprafacial fasion in thermally allowed [3,3]sigmatropic rearrangement: 4-centered chair-form and 6-centered boat-form. In view of the Cope[5a,9] and the Claisen[5b,10] rearrangements attained so far, we can reasonably formulate the transition state topology of choice for the allylic rearrangement of trichloroacetimidate as the former in agreement with Overman. Furthermore, the finding that the *R-E* trichloroacetimidate (+)-**2** rearranged to give the *R-E* trichloroacetamide (+)-**3** cogently supports the fashion **6**. The *S-Z* product, which would be expected from the alternative 4-centered mode **7**, was not detected at all in the present rearrangement. The preference of fashion **6** to **7** could be rationalized by the unfavorable non-bonded interaction between methyl group and hydrogen atom which orient *syn*-axial in the latter,

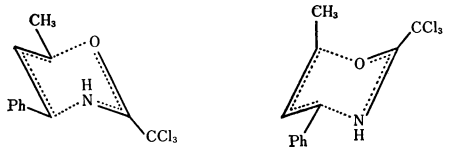


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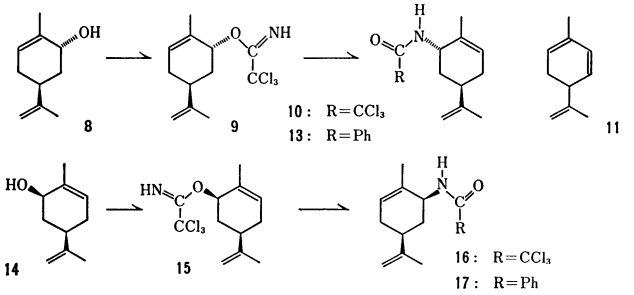
Fig. 1. Transition state topology predicted for the rearrangement of (2*E*)-(1*R*)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate [(+)-**2**].

while both methyl and phenyl groups orient equatorial in the former, therefore thermodynamically more favorable.

As a probe of synthetic utility, the present rearrangement was successfully applied to the naturally derived allylic alcohols whose configurations have been known. According to Scheme 2, (+)-*trans*-carveol [(+)-**8**, α_D^{20} 172°][11] was converted into the corresponding trichloroacetimidate [(+)-**9**, $[\alpha]_D^{22}$ 72°] in 85% yield. It is noted in this system that the allylic group is tied back in a 6-membered ring, which *a priori* compels the transition state topology to assume nothing but a doubly suprafacial mode.



Scheme 2.

Upon heating, (+)-**9** gave (−)-*N*-carveyl trichloroacetamide [(−)-**10**, $[\alpha]_D^{23}$ −117°] in 44% yield. The observed lowering in the yield of rearrangement product may be attributed to the elimination side process, as actually indicated by the formation of the triene (**11**, 18%) and trichloroacetamide (**12**, 41%).[12] The transformation of (−)-**10** by the consecutive alkaline hydrolysis and benzoylation gave (−)-*N*-*trans*-carveylbenzamide [(−)-**13**, $[\alpha]_D^{18}$ −245°, mp 112—113 °C]. The absolute configuration of (−)-**13** can be safely assigned as depicted in Scheme 2 by the comparison of physical constants in agreement with those in the literature.[13]

In the case of the (−)-*cis* counterpart [(−)-**15**, $[\alpha]_D^{23}$ −48 °], (−)-*N*-carveyltrichloroacetamide [(−)-**16**,$[\alpha]_D^{23}$ −43.6°] was obtained in 42% yield along with **12** (35%). By exactly the same work-up as for (−)-*trans* isomer, (−)-**16**, was transformed into (−)-*N*-*cis*-carveylbenzamide [(−)-**17**, $[\alpha]_D^{20}$ −95.2°, mp 169 °C].[13]

In both cases, the absolute configurations of the rearrangement products coincided with those predicted from the doubly suprafacial transition state. The stereospecific 1,3-transposition of alcohol and amine functions was thus achieved by the present self-immolative asymmetric synthesis.

Experimental

All melting and boiling points were uncorrected. IR spectra were recorded with a Hitachi 215 and NMR spectra on a Varian EM-360. Elemental analyses were carried out with a Yanagimoto CHN-corder TM-1. Optical rotations were observed with a Yanagimoto OR-50 or a Perkin Elmer R-241.

Assessment of the Enantiomeric Purity of (E)-(+)-4-Phenyl-3-buten-2-ol [(+)-1]. Chemical shift non-equivalence of the enantiomers was observed on the following conditions; carbon tetrachloride solution of (+)-**1** (0.45 M, $[\alpha]_D^{20}$ 17.3°)[7a,b] and tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]-europium (III) (**18**, 0.06 M) using JEOL MH-100 (100 MHz). Methyl doublets of enantiomers appeared at (δ 2.31, 2.37) and (δ 2.34, 2.40) respectively. The enantiomeric purity of (+)-**1** proved to be 45±2% by the calculation from peak heights and areas.

(E)-(+)-1-Methyl-3-phenyl-2-propenyl Trichloroacetimidate [(+)-2]. A solution of (+)-**1** [1.8 g, 12 mmol, $[\alpha]_D^{20}$ 17.3° (*c* 5.1, $CHCl_3$)] in dry ether (20 ml) was treated with sodium hydride (110 mg, 47% in mineral oil, 2.1 mmol) which had been previously washed 3 times with dry hexane. The resulting mixture was added to trichloroacetonitrile (1.8 g, 12 mmol) in dry ether (10 ml) at −15 °C in nitrogen atmosphere. After stirring at 0 °C for 1.5 h, the solution was concentrated under reduced pressure. Pentane (40 ml) containing methanol (0.8 ml, 2.1 mmol) was added and the mixture was shaken for 1 min. Successive filtration and evaporation gave (+)-**2** (3.3 g, 94%) whose purity proved to be 85% as assessed by NMR; $[\alpha]_D^{20}$ 34.7° (*c* 5.0, $CHCl_3$); IR (liquid): NH 3350, C=N 1650, =CH (*E*) 960 cm^{-1}; NMR (CCl_4): δ 1.63 (d, 3H, CH_3), 5.77—6.28 (m, 1H, CH), 6.39—7.33 (m, 2H, CH=CH), 7.57—8.00 (m, 5H, phenyl), 8.70—9.00 (broad, 1H, NH).

[3,3] Rearrangement of (+)-2. The trichloroacetimidate (+)-**2** (3.2 g, purity 85%) in toluene (35 ml) was heated under reflux for 4 h. Distillation gave (+)-*N*-[(*E*)-1-phenyl-2-butenyl]trichloroacetamide [(+)-**3**, 2.0 g, 74%]; bp 121—124 °C/0.06 Torr; mp 62—64 °C; $[\alpha]_D^{20}$ 15.1° (*c* 2.7, $CHCl_3$); IR (KBr): NH 3400, C=O 1680, =CH (*E*) 962 cm^{-1}; NMR (CCl_4): δ 1.70—1.91 (m, 3H, CH_3), 5.28—5.87 (m, 3H, CH, and CH=CH), 6.44—7.00 (broad, 1H, NH), 7.31 (s, 5H, phenyl).

Found: C, 49.30; H, 4.18; N, 4.76%. Calcd for $C_{12}H_{12}NOCl_3$: C, 49.26; H, 4.13; N, 4.79%.

Hydrogenation of (+)-3. The trichloroacetamide (+)-**3** (1.0 g, 3.4 mmol) was hydrogenated over 5% palladium-charcoal (200 mg) in ethanol (100 ml) and 2 equivalent amounts of hydrogen (170 ml at room temperature) were absorbed. The reaction mixture was neutralized with aqueous potassium carbonate. Distillation gave (+)-*N*-(1-phenylbutyl)dichloroacetamide [(+)-**4**, 740 mg, 83%]; bp 116 °C/0.03 Torr; mp 92—93.5 °C; $[\alpha]_D^{20}$ 32.7° (*c* 3.0, $CHCl_3$); IR (KBr): NH 3280, C=O 1660 cm^{-1}; NMR ($CDCl_3$): δ 0.78—1.12 (m, 3H, CH_3), 1.13—2.08 (m, 4H, CH_2CH_2), 4.78—5.20 (m, 1H, CH), 5.98 (s, 1H, $CHCl_2$), 7.41 (s, 5H, phenyl).

Found: C, 55.34; H, 6.07; N, 5.39%. Calcd for $C_{12}H_{15}NOCl_2$: C, 55.40; H, 5.81; N, 5.38%.

(−)-1-Phenyl-1-aminobutane [(−)-5]. The racemic amine[14] (136 g, 0.91 mol) was added to (−)-*N*-acetylleucine (158 g, 0.91 mol) in methanol (1200 ml) and the salt formed was recrystallized 4 times from methanol to yield colorless fine needles (4.6 g); mp 196—198 °C; $[\alpha]_D^{25}$ −1.8° (*c* 5.0, methanol). The physical constants did not alter on further recrystallizations. The amine liberated from the salt had bp 105—107 °C/20 Torr, $[\alpha]_D^{25}$ −22.2° (*c* 5.1, $CHCl_3$). The racemic **5** exhibited an apparent chemical shift non-equiva-

lence for the methine proton in carbon tetrachloride solution of (±)-**5** (0.4 M) and **18** (0.02 M), whereas no separation of the same signal was observed with the resolved amine under the same conditions.

(−)-N-(1-Phenylbutyl)dichloroacetamide [*(−)-4*]. To the solution of dichloroacetyl chloride (1.5 g, 10 mmol) in benzene (10 ml), the mixture of (−)-**5** (1.5 g, 10 mmol) and pyridine (1.6 g, 20 mmol) in benzene (10 ml) was added dropwise at 0 °C. After stirring at room temperature overnight, the resulting dichloroacetamide was extracted with benzene. Distillation gave (−)-**4** (1.7 g, 56%); $[\alpha]_D^{25}$ −71.7° (*c* 3.1, $CHCl_3$).

*(+)-*trans*-Carveyltrichloroacetimidate* [*(+)-9*]. The reaction of (+)-*trans*-carveol [(+)-**8**, 1.5 g, 10 mmol, α_D^{20} 172° (neat) (lit,[11] α_D^{20} 185.8°)] and trichloroacetonitrile (1.4 g, 10 mmol) was conducted with potassium hydride (500 mg, 23.8% in mineral oil, 2 mmol) in place of sodium hydride. The subsequent work-up in exactly the same manner as described for (+)-**2** yielded (+)-**9** (2.5 g, 85%). In this case, the unreacted (+)-**8** was not detected in NMR spectrum; $[\alpha]_D^{22}$ 72° (*c* 3.0, $CHCl_3$); IR (liquid): NH 3350, C=N 1650 cm^{-1}; NMR (CCl_4): δ 0.68—2.75 (m, 5H, ring protons), 1.78 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 4.78—4.99 (m, 2H, $=CH_2$), 5.41—5.66 (m, 1H, CH–O), 5.77—6.07 (m, 1H, =CH–), 8.33—8.63 (broad, 1H, NH).

[3,3] Rearrangement of (+)-9. The trichloroacetimidate (+)-**9** (2.5 g) in toluene (25 g) was heated under reflux for 10 h. The reaction mixture was concentrated and treated with warm hexane. After removal of the insoluble material, trichloroacetamide (**12**, 560 mg, 41%), the solution was evaporated. After 1,5,8(9)-*p*-menthatriene (**11**, 200 mg, 18%) was removed, (−)-*N*-carveyltrichloroacetamide [(−)-**10**, 1.1 g, 44%] distilled at 114—115 °C/0.15 Torr. The analytical sample was obtained by recrystallization from hexane; mp 91—93 °C; $[\alpha]_D^{23}$ −117° (*c* 3.0, $CHCl_3$); IR (KBr): NH 3310, C=O 1690 cm^{-1}; NMR (CCl_4): δ 1.20—2.58 (m, 5H, ring protons), 1.80 (s, 6H, $2CH_3$), 4.28—4.66 (m, 1H, CH–N), 4.85—5.00 (m, 2H, $=CH_2$), 5.79—6.01 (m, 1H, =CH–), 6.40—6.83 (broad, 1H, NH).

Found: C, 48.55; H, 5.58; N, 4.69%. Calcd for $C_{12}H_{16}NOCl_3$: C, 48.59; H, 5.44; N, 4.72%.

*(−)-N-*trans*-Carveylbenzamide* [*(−)-13*]. Sodium hydroxide (1.6 g, 40 mmol) in water (8 ml) was added to (−)-**10** (400 mg, 1.4 mmol) in ethanol (13 ml). The reaction mixture was stirred in nitrogen atmosphere at room temperature for 40 h. The amine extracted with ether was treated with benzoyl chloride (420 mg, 3 mmol) in pyridine (3 ml). The resulting benzamide (−)-**13** was extracted with chloroform and recrystallized from methanol–water; mp 112—113 °C; $[\alpha]_D^{18}$ −245° (*c* 3.0, $CHCl_3$) (lit,[13a] mp 103 °C; $[\alpha]_D^{21}$ −175.4°, lit,[13b] 114 °C; $[\alpha]_D$ −250°).

Found: C, 79.76; H, 8.36; N, 5.41%. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%.

*(−)-*cis*-Carveyltrichloroacetimidate* [*(−)-15*]. By the same procedure as described for the (+)-*trans* counterpart, (−)-*cis*-carveol [(−)-**14**, α_D^{24} −22° (neat) (lit,[15a] α_D^{25} −22.8°)] was converted to (−)-**15** (99%); $[\alpha]_D^{23}$ −48° (*c* 3.0, $CHCl_3$); IR (liquid): NH 3350, C=N 1660 cm^{-1}; NMR (CCl_4): δ 0.87—2.80 (m, 5H, ring protons), 1.85 (s, 6H, $2CH_3$), 4.97—5.18 (m, 2H, $=CH_2$), 5.71—6.19 (m, 2H, CH–O and =CH–), 8.71—8.95 (broad, 1H, NH).

[3,3] Rearrangement of (−)-15. The trichloroacetimidate (−)-**15** (2.6 g) in xylene (26 ml) was heated under reflux for 8 h. The reaction mixture was worked up in exactly the same manner as described for (−)-**10**. Along with **12** (500 mg, 35%), (−)-*N*-carveyltrichloroacetamide [(−)-**16**] was obtained (1.1 g, 42%); bp 109—110 °C/0.1 Torr; mp 87—89° C; $[\alpha]_D^{23}$ −43.6° (*c* 3.0, $CHCl_3$); IR (KBr): NH 3270, C=O 1680 cm^{-1}; NMR (CCl_4): δ 1.05—2.63 (m, 5H, ring protons), 1.73 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 4.26—4.75 (m, 1H, CH–N), 4.73—4.93 (m, 2H, $=CH_2$), 5.52—5.87 (m, 1H, =CH–), 6.35—6.93 (broad, 1H, NH).

Found: C, 48.82; H, 5.54; N, 4.77%. Calcd for $C_{12}H_{16}NOCl_3$: C, 48.59; H, 5.44; N, 4.72%.

*(−)-N-*cis*-Carveylbenzamide* [*(−)-17*]. By the same procedure as described for (−)-**14**, (−)-**16** was converted to (−)-**17**; mp 169 °C; $[\alpha]_D^{20}$ −95.2° (*c* 4.7, $CHCl_3$) (lit,[13a] mp 169 °C; $[\alpha]_D^{19}$ −91.9°, lit,[13b] mp 169 °C; $[\alpha]_D$ −96°).

Found: C, 79.97; H, 8.24; N, 5.66%. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%.

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References

1) M. Moriwaki, Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, **41**, 300 (1976).

2) Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, **41**, 303 (1976).

3) a) R. M. Roberts and F. A. Hussein, *J. Am. Chem. Soc.*, **82**, 1950 (1960); b) J. W. Schulenberg and S. Archer, "Organic Reactions," Vol. 14, John Wiley & Sons, New York (1965), p. 28; c) O. Mumm and F. Möller, *Ber.*, **70**, 2214 (1937); d) W. M. Lauer and C. S. Benton, *J. Org. Chem.*, **24**, 804 (1959).

4) M. E. Synerholm, N. W. Gilman, J. W. Morgan, and R. K. Hill, *J. Org. Chem.*, **33**, 1111 (1968).

5) a) R. K. Hill and N. W. Gilman, *Chem. Commun.*, **1967**, 619; b) R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37**, 3737 (1972).

6) a) L. E. Overman, *J. Am. Chem. Soc.*, **96**, 597 (1974); b) L. E. Overman, *Tetrahedron Lett.*, **1975**, 1149; c) L. E. Overman, private communication.

7) a) J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, **1936**, 85; b) H. L. Goering, G. S. Koermer, and E. C. Linsay, *J. Am. Chem. Soc.*, **93**, 1230 (1971); c) O. Červinka, E. Kroupová, and O. Bělovský, *Collect. Czech. Chem. Commun.*, **33**, 3551 (1968).

8) a) P. A. Levene, A. Rothen, and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937); b) O. Červinka, V. Suchan, O. Kotýnek, and V. Dudek, *Collect. Czech. Chem. Commun.*, **30**, 2484 (1965).

9) a) W. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962); b) M. Simonetta, G. Favini, C. Mariani, and P. Gramaccioni, *J. Am. Chem. Soc.*, **90**, 1280 (1968).

10) a) E. N. Marvell, J. L. Stephenson, and J. Ong, *J. Am. Chem. Soc.*, **87**, 1267 (1965); b) Gy. Fráter, A. Habich, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **52**, 335 (1969).

11) S. Schroeter, *Justus Liebigs Ann. Chem.*, **674**, 118 (1964).

12) The yield of **11** lower than that of **12** can be ascribed to the loss during the purification work-up because of the high volatility of **11**.

13) a) H. Goldschmidt and A. Fischer, *Ber.*, **30**, 2069 (1897); b) S. Schroeter and E. L. Eliel, *J. Am. Chem. Soc.*, **86**, 2066 (1964).

14) The racemic amine was obtained from *n*-butyrophenone and ammonium formate; bp 109—111 °C/21 Torr. [bp 107—109 °C/16 Torr; M. Busch and L. Leefhelm, *J. Prakt. Chem.*, **77**, 1 (1908)].

15) a) R. G. Johnston and J. Read, *J. Chem. Soc.*, **1934**, 233; b) R. H. Reitsema, *J. Am. Chem. Soc.*, **75**, 1996 (1953).