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Application of modified hydroxyl-directed diastereodifferentiating Simmons–Smith reaction to an unreactive conjugated triene. Stereocontrolled tandem cyclopropanation–Cope rearrangement–cyclopropanation

Takahiro Tei, Takashi Sugimura,* Toshifumi Katagiri, Akira Tai and Tadashi Okuyama

Faculty of Science, Himeji Institute of Technology, Kohto, Kamigori, Ako-gun, Hyogo 678-1297, Japan

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Abstract—The procedure for the hydroxyl-directed zinc carbenoid addition was applied to a one-pot tandem cyclopropanation–Cope rearrangement–cyclopropanation of a cycloheptatriene derivative to afford a stereochemically pure tricyclic compound in high yield.

1. Introduction

The hydroxyl-directed cyclopropanation of allylic and homoallylic alcohols with zinc carbenoid can be easily performed simply by adding diiodomethane to a mixture of the alcohol and diethylzinc in diethyl ether.[1] However, when the hydroxyl group is separated by more bonds from the olefinic site, the degree of diastereodifferentiation is significantly dependant on the reaction conditions, due to competition from a non-directed intermolecular reaction. Almost no diastereoselectivity is seen in the reaction of **1a** (where the hydroxyl group and double bond are separated by five bonds) under the conventionally employed conditions,[2a,c] but the selectivity is dramatically improved by the modified method (very slow addition of CH_2I_2 to a mixture of **1a** and Et_2Zn in diethyl ether) to give product with d.e. of 97% (% d.e. = 100 (**2**–**3**)/(**2**+**3**)).[3] The reaction of **1b**, which has a bulky chiral auxiliary **b** instead of **a**, gives 99% d.e. even under the standard conditions.[2b,c] The improvement in the selectivity of the reaction of **1a** is ascribed to the effective formation of active zinc carbenoids at the hydroxy group, and thus the undesired intermolecular addition is interrupted.[3,4]

The diastereodifferentiating cyclopropanation of **4** should be a more difficult case to obtain the desired product due to poor reactivity of the conjugated triene unit in **4**. In fact, the cyclopropanation of **4d** proceeded only with reactive dihalocarbenes,[5] whereas **1d** is one of the best substrates for the electrophilic addition, and cyclopropanated products are obtained in good yields with various carbenoids.[6] Since the stereospecific and irreversible rearrangement of **5** to **6** is known,[5] the hydroxyl-directed cyclopropanation of **4a** or **4b** is a key process in obtaining optically active cyclopropane-fused compounds such as **7**. Herein, we would like to report that the combination of the modified method and the chiral auxiliary **b** is effective not only for high levels of stereocontrol but also for promoting the cyclopropanation of an unreactive triene substrate.

2. Results and discussion

Substrates **4a** and **4b** were prepared by the reported method.[5] The unreactive nature of **4** to zinc carbenoid was confirmed with **4c**, where the hydroxy group is protected. No cyclopropanation of **4c** took place even under varied zinc carbenoid reaction conditions with large excesses of the reagents. Thus, the non-hydroxyl-directed reaction of **4** with zinc carbenoid is much slower than the decomposition of the zinc carbenoid.

In contrast, the cyclopropanation of **4a** and **4b**, bearing a hydroxy group, proceeded with zinc carbenoid, although the reaction was not as smooth as that of **1** which has an unconjugated olefin.[7] When **4a** was

* Corresponding author. Tel.: +81-791-58-0168; fax: +81-791-58-0115; e-mail: sugimura@sci.himeji-tech.ac.jp

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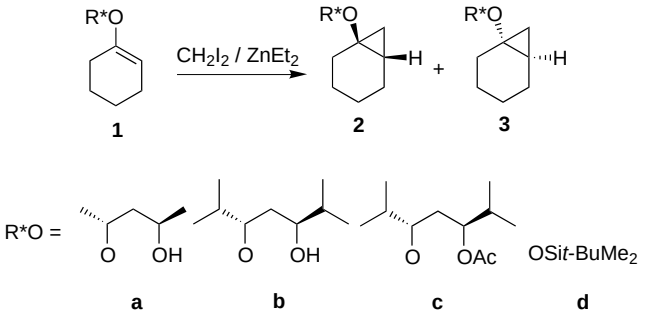
treated with diethylzinc (5 equiv.) and diiodomethane (12 equiv.) at room temperature according to the standard procedure, a complex mixture including unreacted **4a** was obtained in all solvents employed (hexane, diethyl ether, and THF) after 24 h. The mixture contained several isomers of both the bis- and tris-cyclopropanation products, as deduced from ^{1}H NMR and GC–MS analyses. The results were improved with **4b** having a bulky auxiliary; the reaction in diethyl ether gave a mixture of **7b** and a side-product **8b** in 34% yield at a ratio of 2/1 along with some accompanying products. The side-product **8** must be formed from the norcaradiene tautomer of **4**.

By applying the modified method, both improvement of the yield of **7** and minimization of the formation of **8** were achieved. Slow addition of diiodomethane (7–12 equiv.) to a mixture of **4a** and diethylzinc (7–12 equiv.) in diethyl ether over 1–3 h resulted in a mixture of **7a** and **8a** in 40–70% yield with recovered **4a** in 10–50%. The ratio of **7a**:**8a** was ca. 2:1. The reaction of **4b** was more efficient under the modified conditions, and was completed with 5–6 equiv. of diethylzinc and 2–2.5 equiv. of diiodomethane. The reaction mixture contained only **7b** and **8b** based on the ^{1}H NMR analysis

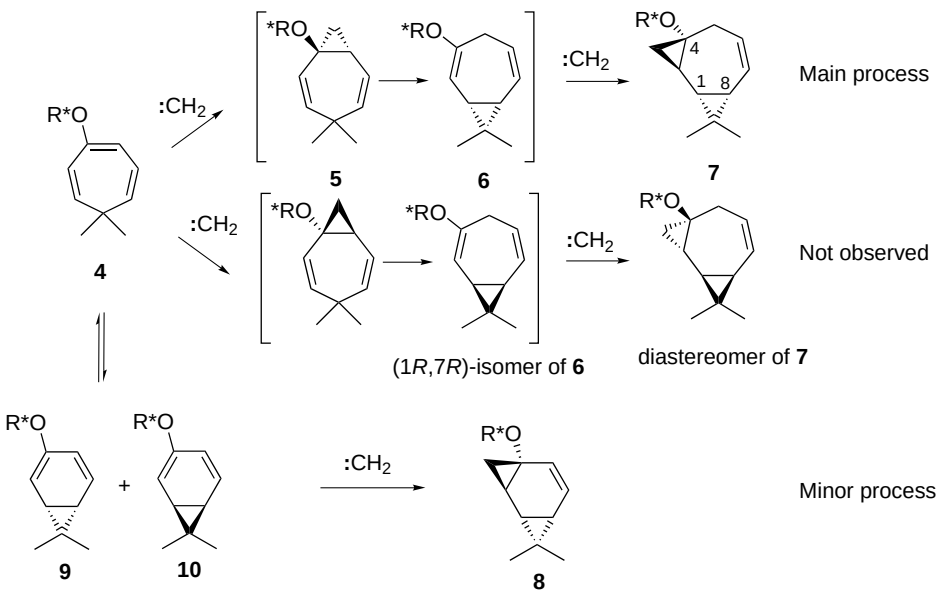


Scheme 1. Cyclopropanation of unconjugated olefins.

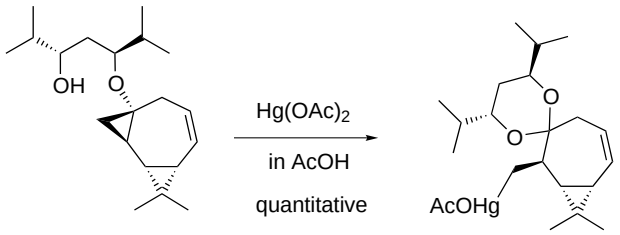
(>90% yield), and the ratio **7b**:**8b** was improved to 4.0:1.

The reactions of **4a** or **4b** using the modified method did not give any detectable diastereomers of **7** or **8**. The stereochemistry of **7b** is expected to be (1*S*,2*R*,4*R*,8*S*) from the stereochemical outcome of the reaction of **1**[2] (see Scheme 1) and the stereospecific Cope rearrangement through a cisoid transition state.[5] This assignment was confirmed by chemical correlation. That is, dichlorocarbene addition to the independently prepared **6b**, the stereochemistry of which was determined to be (1*S*,7*S*),[5] gave a single product (63%). The ring fusion of which should be *exo* due to the very high steric repulsion between dichlorocarbene and the dimethylcyclopropane during the *endo* fusion. Dehalogenation with sodium in methanol–water gave a product identical to **7b** (51%). A diastereomer of **7b** was also prepared by the same procedure from the (1*R*,7*R*)-isomer of **6b**. The diastereomer of **7b** is distinguishable from **7b** and was not detected in the reaction mixture of **4b**. Since the ^{1}H NMR of **7a** is very similar to that of **7b** except for the chiral diol part, the stereochemistry of the ring fusion can be assigned to be the same.

Stereocontrol during the formation of the side-product **8** can be explained as follows. Cycloheptatriene **4** (Scheme 2) is expected to undergo rapid and reversible tautomerization to two diastereomeric norcaradienes, **9** and **10**. Since **9** should be more reactive than **10** in the reaction directed by the chiral hydroxy side chain, **8** was produced free of its diastereomer. The ratio of **7** and **8** is attributable to the mode of the initial zinc carbenoid reaction, because a longer reaction time or repeated additions of the reagents did not affect the ratio. The preferential formation of **7b** in the reaction of **4b** under the modified method indicates that the effective formation of the active species at the hydroxy group promotes the formation of **7** and minimizes the



Scheme 2. Cyclopropanation of conjugated trienes **4**.



Scheme 3. Oxymercuration of **7b**.

reaction with the less populated but more reactive diene **9**.

The obtained **7b** (Scheme 3) is considered to be a useful chiral synthon for several terpenes having a dimethylcyclopropane-fused cycloheptane skeleton such as cyclocolorenone. A key step for synthetic application involves the selective cleavage of the cyclopropyl ether to remove the chiral auxiliary and to convert it into other functional groups. Treatment of **7** with $Hg(OAc)_2$ in acetic acid at room temperature resulted in quantitative formation of **11**.[8] The cleavage of the cyclopropyl ether in preference to the olefin occurs due to effective trapping of the mercury adduct with the intramolecular hydroxyl group, and indicates an additional advantage of the diol auxiliary for the present synthesis.

3. Conclusion

The unreactive nature of **4** toward the zinc carbenoid was overcome by the combination of the modified method and the bulky auxiliary **b**. The results indicate the importance of the effective formation of the active zinc carbenoid for the hydroxyl-directed cyclopropanation when the desired *quasi*-intramolecular addition is not fast enough compared with the decomposition of the reagents as well as side reactions. Application of the present system to the synthesis of optically active sesquiterpenes having a dimethylcyclopropane unit is now in progress.

4. Experimental

4.1. Preparation of the substrates 4

Cycloheptatrienes **4a** and **4b** were prepared by the reported method.[5] Treatment of **4b** (210 mg) with acetic anhydride (0.5 mL) in pyridine (2 mL), followed by extraction and short silica gel column chromatography, afforded **4c** as a colorless oil (231 mg, 95%). $[\alpha]_D^{20} = -32.3$ (*c* 1.6, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (dd, $J=10.3$, 7.3 Hz, 1H), 5.91 (d, $J=10.7$ Hz, 1H), 5.76 (d, $J=7.3$ Hz, 1H), 5.28 (d, $J=10.7$ Hz, 1H), 4.95 (d, $J=10.3$ Hz, 1H), 4.90 (m, 1H), 3.89 (m, 1H), 2.07–1.94 (m, 1H), 2.00 (s, 3H), 1.84 (dd, $J=13.7$, 6.8 Hz, 1H), 1.66 (td, $J=7.8$, 3.4 Hz, 2H), 1.05 (s, 3H), 0.94 (s, 3H), 0.88–0.84 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 157.5, 135.99, 135.96, 129.4, 122.4, 107.9, 78.5, 75.6, 34.9, 32.1, 31.9, 31.0, 30.3, 27.3, 25.1, 18.2, 17.9, 17.6, 16.9; IR (neat, cm^{-1}) 1732; HREI-MS: found: m/z 320.2396; calcd for $C_{20}H_{32}O_3$: 320.2351.

4.2. Cyclopropanation of 4a under the modified conditions

To a solution of **4a** (65 mg) in dry diethyl ether (2 mL) was added a solution of diethylzinc (1 M, 1.6 mL, 6.0 equiv.) at room temperature, the resulting solution was then treated with a solution of diiodomethane (0.07 mL, 3.0 equiv.) in ether (5 mL) was added dropwise in 15 min. After 7 h, the additions of the reagents were repeated. Extraction of the reaction mixture after stirring for an additional 3 h gave a colorless oil (79 mg) consisting of **4a**, **7a**, and **8a** in a ratio of 0.34:1:0.43. Silica gel column chromatography (elution with 30% ethyl acetate in hexane) gave fractions rich in **7a** (45 mg) and rich in **8a** (26 mg). Preparative GPC (JAIGEL-1H+2H, elution with THF) recycling for 20 h of the first faction gave 21 mg of a mixture of **7a** and **8a** (1:0.2) and that of the last fraction gave of **8a** (13 mg). The major product **7a** could not be isolated in a pure form but its ^{1}H NMR was very similar to that of **7b** except for the chiral auxiliary part. Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, $J=9.8$, 7.3, 6.3 Hz, 1H), 5.60 (d, $J=9.8$ Hz, 1H), 4.07 (m, 1H), 4.01 (m, 1H), 3.15 (s, 1H, OH), 2.59 (dd, $J=14.6$, 7.3 Hz, 1H), 2.10 (dd, $J=14.6$, 6.3 Hz, 1H), 1.58 (m, 1H), 1.48 (dd, $J=5.4$, 2.4 Hz, 1H), 1.20–1.12 (m, 7H), 1.07 (s, 3H), 0.98 (s, 3H), 1.06–0.91 (m, 2H), 0.66 (d, $J=7.3$ Hz, 1H), 0.56 (t-like, $J=5.4$ Hz, 1H). Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (d, $J=9.8$ Hz, 1H), 5.41 (dd, $J=9.8$, 4.9 Hz, 1H), 4.11–4.08 (m, 1H), 4.03–3.98 (m, 1H), 2.68 (d, $J=3.4$ Hz, 1H, OH), 1.58 (m, 1H), 1.50–1.44 (m, 2H), 1.25–1.15 (m, 2H), 1.19 (d, $J=5.9$ Hz, 3H), 1.15 (s, 3H), 1.14 (d, $J=5.9$ Hz, 3H), 1.06 (s, 3H), 0.76 (dd, $J=8.9$, 4.9 Hz, 1H), 0.67 (dd, $J=6.3$, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.9, 122.6, 77.2 71.3, 64.4, 45.3, 30.0, 27.8, 25.7, 25.6, 23.8, 23.0, 21.3, 20.4, 15.0; HREI-MS of the acetate analogue: found: m/z 278.1882; calcd for $C_{17}H_{26}O_3$: 278.1827.

4.3. Cyclopropanation of 4b under the modified conditions

To a solution of **4b** (300 mg) in dry diethyl ether (50 mL) was added a solution of diethylzinc (1 M, 6.42 mL, 6.0 equiv.). To this mixture, a solution of diiodomethane (689 mg, 2.4 equiv.) in dry diethyl ether (50 mL) was added dropwise over 90 min. After 14 h stirring, the mixture was extracted to afford a colorless oil (345 mg). Since the separation of **7b** and **8b** by silica gel chromatography was not effective enough, the isolated yield of **7b** remained at 50–70%. Data for **7b**: $[\alpha]_D^{25} = -29.3$ (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (ddtm, $J=9.5$, 7.3, 2.4 Hz, 1H), 5.61 (d, $J=9.5$ Hz, 1H), 3.58–3.52 (m, 2H), 3.21 (d, $J=2.9$ Hz, 1H), 2.64 (dd, $J=14.7$, 7.3 Hz, 1H), 2.11 (dd, $J=14.7$, 6.4 Hz, 1H), 1.96 (q, $J=6.8$ Hz, 1H), 1.65–1.56 (m, 3H), 1.20 (dd, $J=11.0$, 4.9 Hz, 1H), 1.08 (s, 3H), 1.04–1.01 (m, 2H), 0.99 (s, 3H), 0.91 (d, $J=6.9$ Hz,

3H), 0.87 (d, $J=6.8$ Hz, 3H), 0.84 (d, $J=6.8$ Hz, 3H), 0.77 (d, $J=6.8$ Hz, 3H), 0.66 (d, $J=8.3$ Hz, 1H), 0.53 (dd, $J=6.4$, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.1, 128.9, 80.8, 73.3, 69.0, 33.9, 32.7, 31.2, 29.8, 27.8, 27.2, 26.4, 24.3, 20.1, 20.0, 18.4, 18.4, 18.0, 17.5, 17.2; HREI-MS: found: m/z 306.2509; calcd for $C_{20}H_{34}O_2$: 306.2559.

4.4. Stereochemical determination of 7b

To a solution of **6b** (1*S*,7*S*-isomer, 15.8 mg) in chloroform (7 mL) was added benzyltriethylammonium chloride (0.5 mg) and 50% aqueous NaOH (230 mg) at 0°C. After stirring for 30 min at room temperature, the mixture was extracted and purified by silica gel chromatography to give a colorless oil (11.5 mg, 61% yield). $[\alpha]_D^{25}=-46.8$ (c 0.6, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (m, 1H), 5.59 (d, $J=9.8$ Hz, 1H), 3.78 (m, 1H), 3.54 (m, 1H), 2.80 (m, 1H), 2.15 (dd, $J=14.9$, 7.6 Hz, 1H), 2.03 (m, 1H), 1.62 (brs, 1H), 1.60 (m, 1H), 1.49 (m, 1H), 1.34 (m, 1H), 1.17 (s, 3H), 1.14 (m, 1H), 1.03 (s, 3H), 0.92 (d, $J=6.8$ Hz, 6H), 0.89 (d, $J=6.6$ Hz, 3H), 0.87 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.9, 128.6, 78.6, 77.3, 72.9, 36.7, 34.7, 34.2, 32.9, 30.3, 27.6, 26.7, 26.4, 24.4, 21.1, 19.6, 18.7, 17.6, 17.5, 16.7. A solution of this compound (6.7 mg) in ether (3 mL) was added a piece of sodium metal followed by continuous addition of a mixture of methanol and water (1:0.03) at 0°C for 24 h. Extraction and silica gel column chromatography (elution with 3% ethyl acetate in hexane) gave a colorless oil (2.8 mg, 51% yield). This product showed identical NMR spectra to that of **7b** as well as the same GLC retention time (62.5 min, PEG-20 M, 50 m, 160°C).

Using the same procedure, (1*R*,7*R*)-isomer of **6b** (6.6 mg) was converted to a dichlorocarbene adduct (4.8 mg, 64% yield). $[\alpha]_D^{25}=-24$ (c 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (m, 1H), 5.57 (d, $J=10.0$ Hz, 1H), 3.78 (m, 1H), 3.65 (m, 1H), 2.81 (m, 1H), 2.59 (dd, $J=15.1$, 7.6 Hz, 1H), 1.95 (d, $J=4.4$ Hz, 1H), 1.89 (m, 1H), 1.78–1.63 (m, 2H), 1.55 (m, 1H), 1.16 (s, 3H), 1.15 (m, 1H), 1.02 (s, 3H), 1.00 (m, 1H), 0.96 (d, $J=6.8$ Hz, 3H), 0.95 (d, $J=6.8$ Hz, 3H), 0.89 (m, 1H), 0.85 (d, $J=6.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.9, 128.5, 79.4, 77.3, 73.4, 71.9, 36.7, 35.1, 34.5, 31.9, 27.5, 26.6, 26.4, 24.4, 21.1, 18.9, 18.4, 18.2, 17.5, 17.2. The diastereomer of **7b** was obtained by reduction with sodium. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (m, 1H), 5.58 (d, $J=12.0$ Hz, 1H), 3.55 (m, 1H), 3.48 (m, 1H), 3.17 (s, 1H), 2.58 (dd, $J=14.2$, 7.1 Hz, 1H), 2.16 (m, 1H), 1.58 (m, 1H), 1.38 (dd, $J=10.9$, 5.5 Hz, 1H), 1.24–1.12 (m, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00–0.94 (m, 2H), 0.92 (d, $J=6.5$ Hz, 3H), 0.91 (d, $J=6.5$ Hz, 3H), 0.88 (d, $J=6.5$ Hz, 3H), 0.82 (d, $J=6.5$ Hz, 3H), 0.70 (d, $J=8.2$ Hz, 1H), 0.57 (dd, $J=6.5$, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.5, 128.6, 77.6, 73.3, 69.1, 34.0, 32.3, 31.9, 30.7, 27.8, 27.5, 26.5, 23.9, 20.3, 20.1, 18.6, 18.5, 18.0, 17.9, 17.2; GLC retention time: 66.5 min (PEG-20 M, 50 m, 160°C).

4.5. Oxymercuration of 7b

To a solution of **7b** (60.0 mg) in acetic acid (7 mL) was added mercury(II) acetate (99.8 mg, 1.6 equiv.). After 2.5 h, the mixture was concentrated under vacuum. The mixture was dissolved in dichloromethane, filtered, and then concentrated to give **11** as a colorless oil (117 mg, crude 106%), which was essentially pure judged by ^{1}H NMR. When the reaction mixture was treated with NaCl before the concentration, a chloromercuro analogue of **11** was obtained by silica gel chromatography (elution with 15% ethyl acetate in hexane) as a colorless oil (42% yield). $[\alpha]_D^{20}=-34$ (c 2.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (m, 1H), 5.64 (s, 1H), 3.68 (dd, $J=13.4$, 6.8 Hz, 1H), 3.63 (ddd, $J=13.2$, 7.3, 5.4 Hz, 1H), 2.78 (dd, $J=12.2$, 5.4 Hz, 1H), 2.53 (dd, $J=12.2$, 6.8 Hz, 1H), 1.93–1.81 (m, 3H), 1.78–1.62 (m, 2H), 1.60 (m, 1H), 1.24 (m, 1H), 1.18 (d, $J=8.9$ Hz, 1H), 1.07 (s, 3H), 1.00 (s, 3H), 0.98 (d, $J=6.8$ Hz, 3H), 0.92 (d, $J=7.3$ Hz, 3H), 0.90 (d, $J=7.3$ Hz, 3H), 0.85 (d, $J=6.8$ Hz, 3H), 0.53 (tlike, $J=8.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.8, 128.6, 98.9, 75.9, 71.1, 44.9, 37.9, 33.4, 32.4, 31.3, 29.2, 28.8, 28.4, 26.4, 18.8, 18.7, 18.5, 18.3, 18.0, 15.7.

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