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Facile Synthesis of Functionalized Bicyclo[3.2.1]octane Systems Using the Selective Fragmentation Reaction

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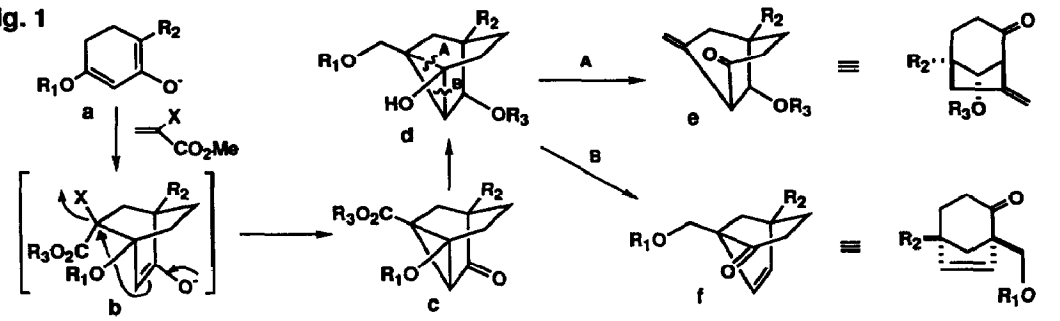
Abstract: A facile synthesis of two different types of functionalized bicyclo[3.2.1]octane systems (kaurane and stachane types) from a tricyclo[3.2.1.$0^{2,7}$]octane derivative was performed using the selective fragmentation reaction.

The construction of bicyclo[3.2.1]octane systems is essential for the total synthesis of cyclic diterpenoids such as kaurene, stachene, gibberellins and grayanotoxins. While conducting research[2] on structurally unique natural products using the sequential Michael reaction and fragmentation reaction in combination, a convenient method for synthesizing two different types of functionalized bicyclo[3.2.1]octane systems by the selective fragmentation of a common tricyclo[3.2.1.$0^{2,7}$]octane derivative was established and applied to the synthetic study of grayanotoxins.

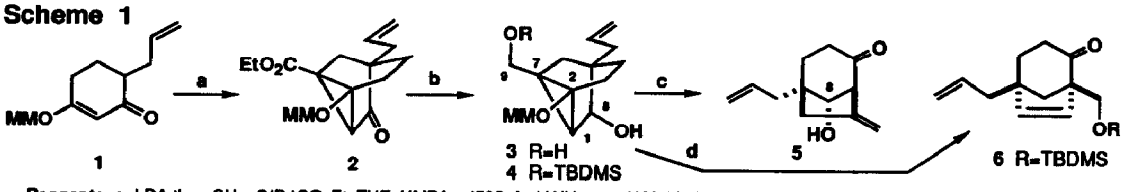
As shown in Fig. 1, cleavage of the A bond of the tricyclo[3.2.1.$0^{2,7}$]octane **d** gives a karane-type bicyclo[3.2.1]octane **e**, while stachane-type bicyclo[3.2.1]octane **f** forms by cleavage of the B bond in **d**. Tricyclic compound **d** is easily obtained from **c** which can be prepared by the sequential Michael-substitution reaction of kinetic enolate **a** of 3-alkoxycyclohexenone with α-haloacrylate through **b**.

Fig. 1



Reaction of a kinetic enolate of **1**[3] with ethyl α-bromoacrylate in THF-HMPA at -45°C afforded adduct **2**[4] in 74% yield (Scheme 1). $LiAlH_4$ reduction of **2** gave diol **3**[5] in 95% yield. When **3** was treated with a catalytic amount of concentrated HCl in MeOH at 25°C, deprotection of the methoxymethyl group followed by fragmentation reaction occurred to give kaurane-type bicyclo[3.2.1]octane derivative **5**[6] in 82% yield. In this fragmentation, cleavage of the bond between C(2) and C(7) is preferable to that of the bond between C(2) and C(1), since the carbon-carbon bond [between C(2) and C(7)] and carbon-oxygen bond at C(9) bearing a leaving hydroxyl group can undergo antiperiplanar arrangement. This does not occur for the carbon-carbon bond [between C(2) and C(1)] and carbon-oxygen bond at C(8). Cleavage of the bond between C(2) and C(1) was

Scheme 1

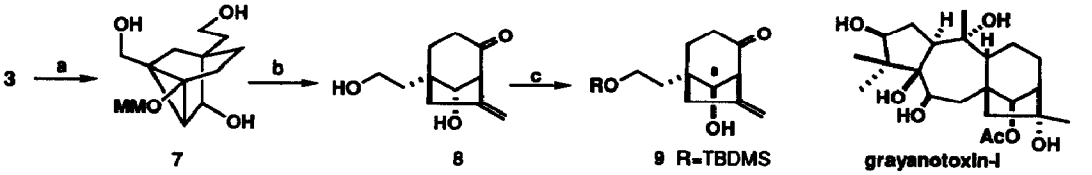


Reagents: a. LDA then CH_2=C(Br)CO_2Et, THF, HMPA, -45°C; b. $LiAlH_4$; c. c.HCl, MeOH, 25°C; d. i) TBDMSCl, DMAP, iPr_2NEt; ii) TsCl, py, then H_2O

carried out by converting the hydroxyl group at C(8) to a tosylate ester. Treatment of **3** with *tert*-butyldimethylsilyl chloride gave monosilyl ether **4**, which, on treatment with *p*-toluenesulfonyl chloride in pyridine followed by exposure to H_2O, gave stachane-type bicyclo[3.2.1]octane **6**[7] in 80% overall yield.

The present method was used to synthesize bicyclo[3.2.1]octane derivative **9**, possessing a β hydroxyl group at C(8) and useful for constructing the functionalized C/D ring system in grayanotoxins. As shown in Scheme 2, **3** was converted to triol **7**, which, when treated with concentrated HCl, gave **8** in 72% overall yield. After protecting the primary hydroxyl group of **8**, the secondary hydroxyl group was inverted by treatment with K_2CO_3 in MeOH to give **9**[8] in 36% overall yield with the recovery of **8** (9:8=2:3).

Scheme 2



Reagents: a. i) O_3 then Me_2S; ii) $NaBH_4$; iii) $LiAlH_4$; b. c. HCl, MeOH, 25°C; c. i) TBDMSCl, DMAP, iPr_2NEt; ii) K_2CO_3, MeOH

References and Notes

1. Present address: Meiji College of Pharmacy, 1-22-1 Yato-cho, Tanashi, Tokyo 188, Japan.
2. For example: Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1988**, *29*, 5945; Nagaoka, H.; Baba, A.; Yamada, Y. *ibid.* **1991**, *32*, 6741; Nagaoka, H.; Shibuya, K.; Yamada, Y. *ibid.* **1993**, *34*, 1501.
3. Enone **1** was prepared from 3-methoxymethyl-2-cyclohexenone by treatment with LDA (1.2 equiv.) and then allyl bromide (1.2 equiv.) in THF at 0°C in 84% yield.
4. **2**; IR (KBr) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ 1.27 (3H, t, 7.1), 1.40 (1H, m), 1.73 (1H, ddd, 13.7, 9.9, 4.1), 2.10 (1H, dd, 14.0, 8.5), 2.15 (1H, d, 13.1), 2.20 (1H, d, 13.1), 2.22 (1H, dd, 14.0, 6.0), 2.40-2.52 (2H, m), 2.78(1H, s), 3.39 (3H, s), 4.20 (2H, q, 7.1), 4.73 (2H, s), 5.05-5.10 (2H, m), 5.30 (1H, m); HREIMS calcd for $C_{16}H_{22}O_5$ (M^+) 294.1467, found 294.1496.
5. **3**; IR (film) 3392, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ 1.26 (1H, dt, 13.4, 4.4), 1.62-1.72 (3H, m), 1.81 (1H, d, 11.6), 2.00 (1H, d, 7.7), 2.04 (1H, brs), 2.23 (1H, dt, 13.0, 4.7), 2.35 (1H, dt, 13.2, 4.4), 3.38 (3H, s), 3.78 (1H, dd, 11.6, 5.5), 3.83 (1H, brd, 11.6), 4.04 (1H, d, 3.6), 4.70 (1H, d, 6.6), 5.01-5.05 (2H, m); HREIMS calcd for $C_{16}H_{22}O_5$ (M^+ - H_2O) 236.1386, found 236.1412.
6. **5**; IR (film) 3432, 1708, 1656, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ 1.68 (1H, dd, 12.9, 9.1), 2.10 (1H, m), 2.17-2.22 (2H, m), 1.81 (1H, d, 11.6), 2.00 (1H, d, 7.7), 2.04 (1H, brs), 2.26 (1H, dd, 13.6, 7.9), 2.45-2.51 (3H, m), 2.64 (1H, dd, 9.5, 6.8) , 3.29 (1H, d, 5.6), 4.17 (1H, brd, 5.6 Hz), 4.92 (1H, s), 5.02 (1H, t, 2.4), 5.08-5.13 (2H, m), 5.85 (1H, m); HREIMS calcd for $C_{16}H_{22}O_5$ (M^+) 192.1150, found 192.1174.
7. **6**; IR (film) 1709, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ 0.03 (6H, s), 0.87 (9H, s), 1.60 (1H, d, 11.0), 1.69 (1H,m), 1.82 (1H, m), 2.24-2.32 (3H, m), 2.36 (1H, dd, 13.9, 6.8), 2.63 (1H, ddd, 17.9, 8.7, 0.5), 3.72 (1H, d, 10.5), 3.85 (1H, d, 10.5), 5.06-5.12 (2H, m), 5.74 (1H, d, 5.6), 5.83 (1H, m), 5.95 (1H, d, 5.6); HREIMS calcd for $C_{18}H_{30}O_2Si$ (M^+ + 1 - Me) 292.1858, found 292.1863.
8. **9**; IR (film) 3402, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *J* in Hz) δ 0.10 (6H, s), 0.91 (3H, s), 3.35 (1H, s), 3.83 (1H, s), 5.02 (1H, s), 5.10 (1H, t, 2.2); EIMS *m/z* 311 (M^+ +1).

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