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Application of palladium-catalyzed cycloalkenylation reaction to terpenoid synthesis—novel approach to tricyclo[5.3.1.$0^{2,6}$]undecane derivative and its transformation into bicyclo[5.3.1]undecane ring system

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Abstract

A novel synthesis of the tricyclo[5.3.1.$0^{2,6}$]undecane compound **16**, basic carbon skeleton of gymnomitrane class of sesquiterpenoids, and the transformation into the bicyclo[5.3.1]undecane derivative **18**, the AB carbon framework of taxol (**6**), have been achieved. Beginning with the bicyclo[3.2.1]octane ring system **2**, prepared from the cross-conjugated silyl enol ether **1** employing palladium-catalyzed cycloalkenylation reaction, the tricyclo[5.3.1.$0^{2,6}$]undecane ring system **16** was synthesized by using samarium-promoted reductive cyclization of **15**. After conversion of **16** to the hydroxy tosylate **17**, basic treatment of **17** afforded the desired bicyclo[5.3.1]undecane derivative **18**. Interestingly, the highly strained oxetane **19** was also obtained together with **18**.

Keywords: terpenoid; cycloalkenylation; palladium; samarium.

The facile assembly of bicyclo[3.2.1]octane compounds has attracted considerable attention of organic chemists since the ring system is the basic framework of numerous biologically active natural products or their metabolites.[1] For instance, the CD ring system of gibberellins,[2] kaurenes,[3] aphidicolin,[4] and so on. We have recently developed a palladium-catalyzed cycloalkenylation reaction for the construction of a highly functionalized bicyclo[3.2.1]octane skeleton, and succeeded in the preparation of some diterpenoids, which possess the bicyclo[3.2.1]octane ring system as the partial structure (Scheme 1).[5]

As further application of the palladium-catalyzed cycloalkenylation reaction, we became interested in the transformation of the bicyclo[3.2.1]octane carbon framework into other bridged polycyclic ring systems. The gymnomitrane class of sesquiterpenoids, such as gymnomitrol (**3**),[6]

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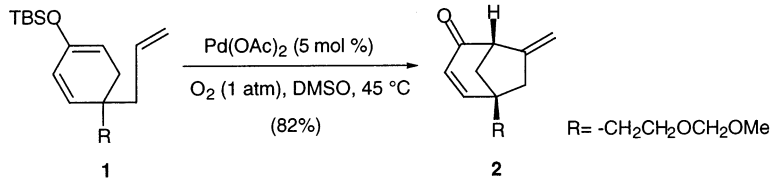


Scheme 1.

gymnomitrene (**4**)[6] and gymnomitrene ketone (**5**),[7] have the tricyclo[5.3.1.$0^{2,6}$]undecane ring system, and consecutive quaternary carbon centers. Because of the challenging structures, several synthetic studies have been reported (Fig. 1).[8]

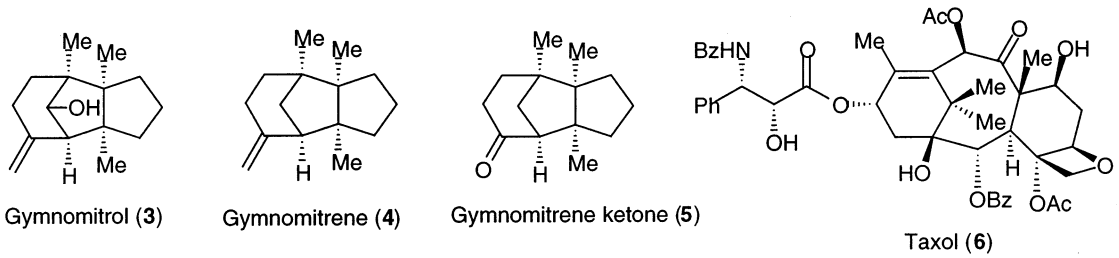
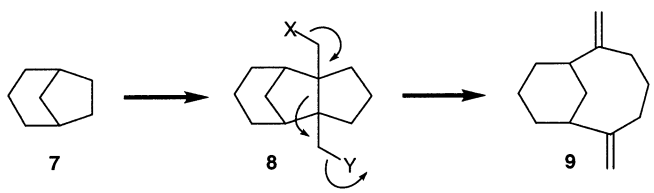


Figure 1.

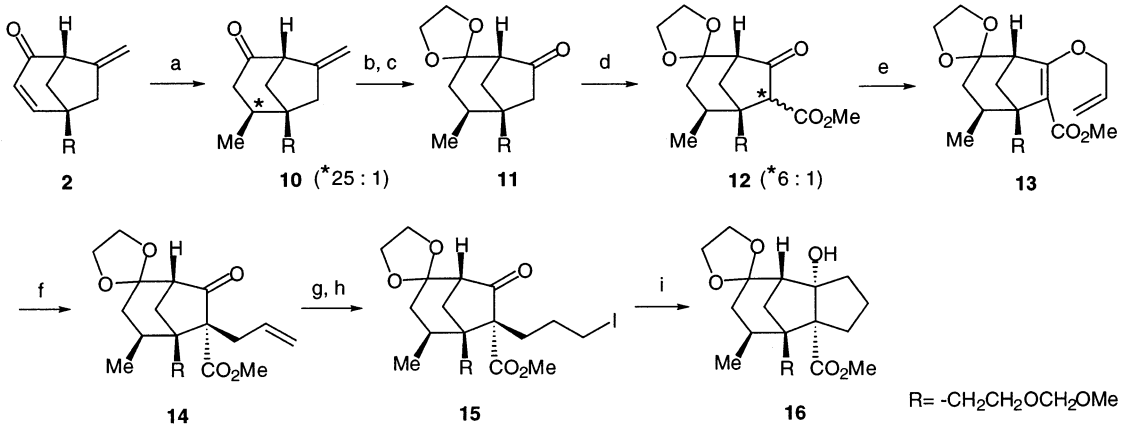
We envisioned that the tricyclo[5.3.1.$0^{2,6}$]undecane carbon skeleton **8**, the basic framework of gymnomitranes, which is available from **7**, could be converted to the bicyclo[5.3.1]undecane compound **9**, the AB carbon framework of taxol (**6**), by the Grob fragmentation reaction shown in Scheme 2.[9] We present herein the outcome of this study, which has resulted in a novel route to gymnomitrane skeleton and the transformation into the AB ring system of taxol (**6**).



Scheme 2.

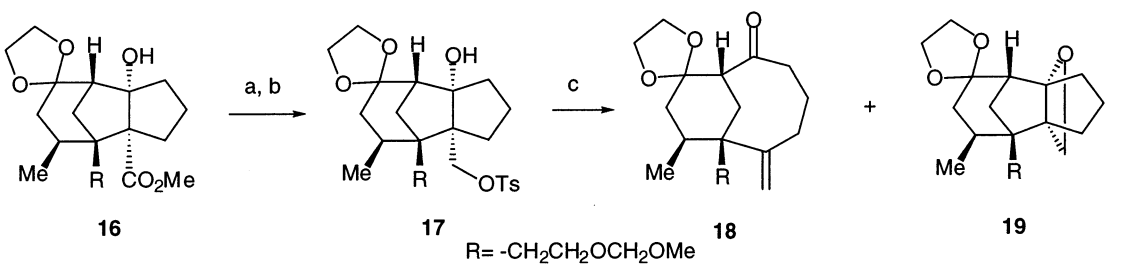
After introduction of methyl group from the convex face of the bicyclo[3.2.1]octane compound **2**, the resulting olefinic ketone **10** (β-Me:α-Me = 25:1) was subjected to acetalization followed by Johnson–Lemieux oxidation[10] to give the ketone **11** as a single stereoisomer after separation. Treatment of **11** with Mander reagent in the presence of LDA furnished the keto ester **12** as a 6:1 mixture. The resulting stereoisomeric mixture **12** was next submitted to allylation to provide **13**, which was heated at 160°C in a sealed tube to afford **14** as a sole product. Functional group manipulation through regioselective hydroboration–oxidation and iodination gave rise to the substrate **15**.

Although tin radical-initiated cyclization of **15** gave no **16**, samarium-promoted reductive cyclization of **15** produced the tricyclo[5.3.1.$0^{2,6}$]undecane derivative **16**[11] in 92% yield. The basic carbon framework of **16** is similar to that of gymnomitranes (Scheme 3).



Scheme 3. Reagents and conditions: (a) Me_2CuLi, Et_2O, −50°C (89%); (b) $HOCH_2CH_2OH$, PPTS, C_6H_6, reflux (93%); (c) OsO_4, $NaIO_4$, Et_2O–H_2O (96%); (d) LDA, THF, −78°C, $NCCO_2Me$ (82%); (e) NaH, HMPA; CH_2=$CHCH_2Br$ (94%); (f) toluene, 160°C, in sealed tube (91%); (g) disiamylborane, THF, 0°C, H_2O_2, NaOH, (76%); (h) I_2, Ph_3P, imidazole, THF–MeCN (92%); (i) SmI_2, THF–HMPA (92%)

Having assembled the requisite skeletal framework, our efforts were focused on the structural transformation of **16**. The ring opening reaction of **16** proved to be more difficult than expected. Ultimately, basic treatments of the hydroxy tosylate **17**, prepared from **16** via $LiAlH_4$ reduction, followed by tosylation, provided the bicyclo[5.3.1]undecane derivative **18**[11] together with the highly strained oxetane **19**[11] (Scheme 4). The structures of **16**, **18**, and **19** were determined by spectroscopies including the NOE experiments, as shown in Fig. 2.



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, reflux (81%); (b) TsCl, pyridine (95%); (c) Method A: KO^{t}Bu, THF, 0°C to rt, **18** (30%), **19** (47%). Method B: $KN(TMS)_2$, THF, 0°C to rt; **18** (32%), **19** (44%)

In conclusion, we have demonstrated a novel approach to the tricyclo[5.3.1.$0^{2,6}$]undecane compound and its transformation into the bicyclo[5.3.1]undecane derivative. Further studies towards the total synthesis of gymnomitrane terpenoid and the application to the preparation of taxol are underway.

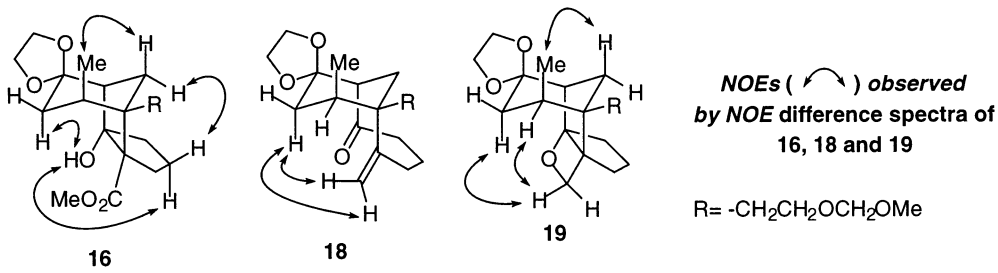


Figure 2.

Acknowledgements

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10. Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.
11. All new compounds reported here were characterized on the basis of their spectral data (^{1}H and ^{13}C NMR, IR, mass, and elemental analysis). Selected spectral data (^{1}H and ^{13}C NMR): Compound **16**; (500 MHz, $CDCl_3$): δ_H 4.90 (1H, s), 4.75 (2H, s), 3.99–3.83 (4H, m), 3.69 (3H, s), 3.57–3.47 (2H, m), 3.34 (3H, s), 2.63 (1H, dq, $J=7.3$ and 7.3 Hz), 2.24 (1H, dd, $J=7.3$ and 14.6 Hz), 2.15 (1H, ddd, $J=2.7$, 5.0 and 13.2 Hz), 2.09 (1H, ddd, $J=2.7$, 6.3 and 13.2 Hz), 2.05 (1H, d, $J=13.2$ Hz), 2.01–1.96 (1H, m), 1.94 (1H, dd, $J=1.8$ and 4.8 Hz), 1.85–1.56 (5H, m), 1.43 (1H, d, $J=1.3$ Hz), 1.40 (1H, br s) and 1.14 (3H, d, $J=7.3$ Hz); (125.65 MHz, $CDCl_3$): δ_C 176.00 (C), 110.46 (C), 96.37 (CH_2), 90.68 (C), 66.02 (C), 64.82 (CH_2), 64.38 (CH_2), 63.36 (CH_2), 55.09 (CH_3), 52.09 (CH), 51.48 (CH_3), 48.45 (C), 45.98 (CH_2), 39.40 (CH_2), 36.40 (CH_2), 33.59 (CH_2), 32.72 (CH), 31.40 (CH_2), 24.98 (CH_2) and 17.69 (CH_3). Compound **18**; (400 MHz, $CDCl_3$): 5.09 (1H, br s), 4.99 (1H, br s), 4.53 (2H, s), 4.03–3.79 (4H, m), 3.34 (1H, ddd, $J=5.6$, 10.0 and 10.0 Hz), 3.31 (3H, s), 3.18 (1H, ddd, $J=5.6$, 10.0 and 10.0 Hz), 2.70 (1H, ddd, $J=3.8$, 12.0 and 12.0 Hz), 2.41–2.14 (7H, m), 2.12–1.96 (3H, m), 1.68–1.50 (2H, m), 1.40 (1H, d, $J=13.6$ Hz), 1.18 (3H, d, $J=7.2$ Hz); (100.63 MHz): δ_C 210.94 (C), 148.58 (C), 116.16 (CH_2), 109.04 (C), 96.39 (CH_2), 64.74 (CH_2), 63.85 (CH_2), 62.96 (CH_2), 56.14 (CH), 55.05 (CH_3), 42.78 (C), 39.82 (CH_2), 35.25 (CH_2), 33.22 (CH_2), 32.13 (CH_2), 30.82 (CH_2), 30.12 (CH), 28.94 (CH_2) and 17.15 (CH_3). Compound **19**; (400 HMz, $CDCl_3$): δ_H 4.55 (2H, s), 4.36 (1H, dd, $J=1.2$ and 7.1 Hz), 4.08 (1H, d, $J=7.1$ Hz), 4.01–3.82 (4H, m), 3.49 (1H, ddd, $J=5.2$, 9.6 and 9.6 Hz), 3.29 (3H, s), 3.25 (1H, ddd, $J=6.0$, 9.6 and 9.6 Hz), 2.80 (1H, dd, $J=8.4$ and 15.2 Hz), 2.25–2.13 (3H, m), 2.04–1.95 (3H, m), 1.87–1.78 (1H, ddd, $J=5.2$, 10.0 and 14.8 Hz), 1.75–1.68 (1H, m), 1.59 (1H, dd, $J=1.5$ and 15.3 Hz), 1.57–1.48 (2H, m), 1.32–1.22 (1H, m), 1.20 (3H, d, $J=6.8$ Hz) and 1.12 (1H, ddd, $J=2.0$, 5.2 and 12.8 Hz); (100.63 MHz, $CDCl_3$): δ_C 110.68 (C), 101.83 (C), 96.38 (CH_2), 71.19 (CH_2), 64.69 (CH_2), 64.43 (CH_2), 63.80 (CH_2), 57.22 (C), 55.10 (CH_3), 50.94 (CH), 45.31 (C), 39.48 (CH_2), 37.78 (CH_2), 35.58 (CH_2), 33.45 (CH_2), 32.44 (CH_2), 32.02 (CH), 26.06 (CH_2) and 19.13 (CH_3).