A New Method for the Synthesis of Baccatin III

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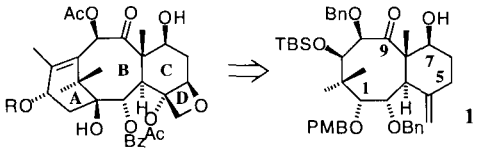
Baccatin III was efficiently synthesized from the BC ring system of Taxol, 2α,10β-dibenzyloxy-11β-(*t*-butyldimethylsilyoxy)-7β-hydroxy-1α-(4-methoxybenzyloxy)-8β,15,15-trimethyl-4-methylene-*trans*-bicyclo[6.4.0]dodecan-9-one (**1**), by successive constructions of A and D rings *via* respective intramolecular pinacol coupling and oxetane forming reaction.

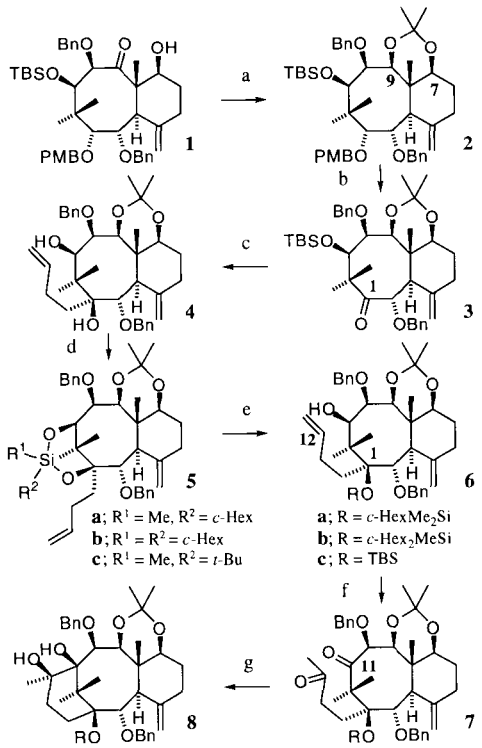
In the previous communication,[1] a stereoselective synthesis of optically active BC ring system of Taxol, a potential synthetic intermediate for the preparation of various taxane derivatives, was described. In this communication, we would like to describe a new method for the synthesis of baccatin III from the BC ring system **1** *via* A ring construction by intramolecular pinacol coupling cyclization of diketone **7** using low-valent titanium reagent, followed by the introduction of C-13 hydroxyl group onto an intermediate **11**, successive stereoselective allylic bromination of **12** and oxetane formation.



R = PhCH(NHBz)CH(OH)CO; **Taxol®**
R = H; **Baccatin III**

Scheme 1.

Since the above mentioned BC ring system **1** is a mixture of slowly interconverting conformational isomers, its related compounds were also anticipated to exist as mixtures of conformational isomers. Then, transformation of **1** to conformationally rigid tricyclic compounds, 7-*O*-,9-*O*-acetonides, was tried in order to confirm the structure of these derivatives conveniently by NMR measurement at room temperature. A mixture of two stereoisomers of the corresponding diols was formed when the aldol **1** was reduced with DIBAL in hexane at room temperature. On the other hand, diastereoselective reduction of the aldol **1** was attained by using AlH_3 in toluene at -78 °C affording the corresponding *cis*-diol preferentially and then protection of thus formed *cis*-diol with isopropylidene acetal provided tricyclic compound **2**. It was converted to conformationally rigid C-1 ketone **3** by deprotection of PMB group and successive oxidation with PDC. Alkylation of C-1 position of **3** with the homoallyllithium reagent in benzene produced the desired bishomoallyl β-alcohol in high yield with perfect diastereoselectivity whereas α-alcohol was obtained preferentially when the reaction was carried out in THF or ether. Deprotection of TBS group resulted in the formation of *cis*-diol **4** and successive treatment of the *cis*-diol **4** with several dialkylsilyl compounds yielded silylene compounds **5a-c** in high yields. Alkylation of these silylene compounds **5a-c** with methyllithium furnished compounds **6a-c** having desired C-1 siloxy groups. Oxidation of thus formed secondary alcohols with a combination of TPAP and NMO gave C-11 ketones in good yields. Oxygenation of C-12 positions of the 8-membered ring ketones proceeded smoothly to produce the desired diketones **7a-c** under forced Wacker oxidation conditions. By the above sequence of manipulations, precursors of the ABC ring system were efficiently synthesized from the BC ring system. The ABC ring systems **8a-c** were obtained by an intramolecular pinacol coupling reaction of the corresponding diketones **7a-c** employing the low-valent titanium reagent prepared from $TiCl_2$ and $LiAlH_4$ as shown in the scheme 2.[2] In this reaction, the desired pinacols **8a-c** were formed as the main products along with small amounts of by-products such as rearranged pinacolone type derivatives. Though the desired pinacol **8a** was obtained up to 71% yield when the cyclization reaction using diketone **7a** was tried, reproducibility of the chemical yield was not always observed. It was probably because property of low-valent titanium reagent depended on the conditions for preparation of the



a; R^1 = Me, R^2 = *c*-Hex
b; R^1 = R^2 = *c*-Hex
c; R^1 = Me, R^2 = *t*-Bu

a; R = *c*-HexMe_2Si
b; R = *c*-Hex$_2$MeSi
c; R = TBS

a) AlH_3, toluene, -78 °C (94%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (100%); b) DDQ, H_2O, CH_2Cl_2, rt (97%); PDC, CH_2Cl_2, rt (90%); c) homoallyl-I, *s*-BuLi, *c*-hexane, benzene, -23 °C to 0 °C (96%); TBAF, THF, 50 °C (100%); d) *c*-HexMeSiCl_2, imidazole, DMF, rt (99% of **5a**); *c*-Hex$_2$Si(OTf)$_2$, pyridine, 0 °C (100% of **5b**); *t*-BuMeSi(OTf)$_2$, pyridine, 0 °C (100% of **5c**); e) MeLi, HMPA, THF, -45 °C (95% of **6a**, 96% of **6b**, 96% of **6c**); f) TPAP, NMO, MS4Å, CH_2Cl_2, CH_3CN, rt (80% from **6a**, 91% from **6b**, 85% from **6c**); $PdCl_2$, H_2O, DMF, rt (98% of **7a**, 92% of **7b**, 91% of **7c**); g) $TiCl_2$, $LiAlH_4$, THF, 40 °C (71-43% of **8a**); 35 °C (63-51% of **8b**); 35 °C (52% of **8c**)

Scheme 2.

titanium species. The intramolecular pinacol coupling reaction using diketones **7a**, **7b** and **7c** gave the corresponding pinacols **8a**, **8b** and **8c** in 71-43%, 63-51% and 52% yields, respectively.

Successive deprotections of **8a-c** with Na/NH_3 and TBAF gave the desired pentaol **9**[3] in high yields (Scheme 3). X-Ray crystallography of the pentaol **9** defined that it possessed the exact stereochemistries of the ABC ring system of baccatin III and Taxol as depicted in Figure 1.

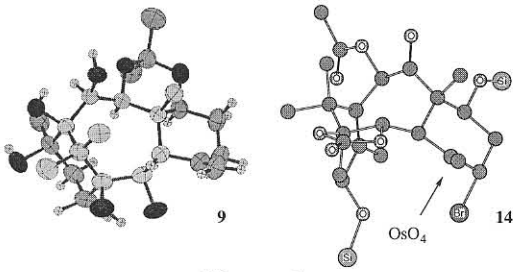
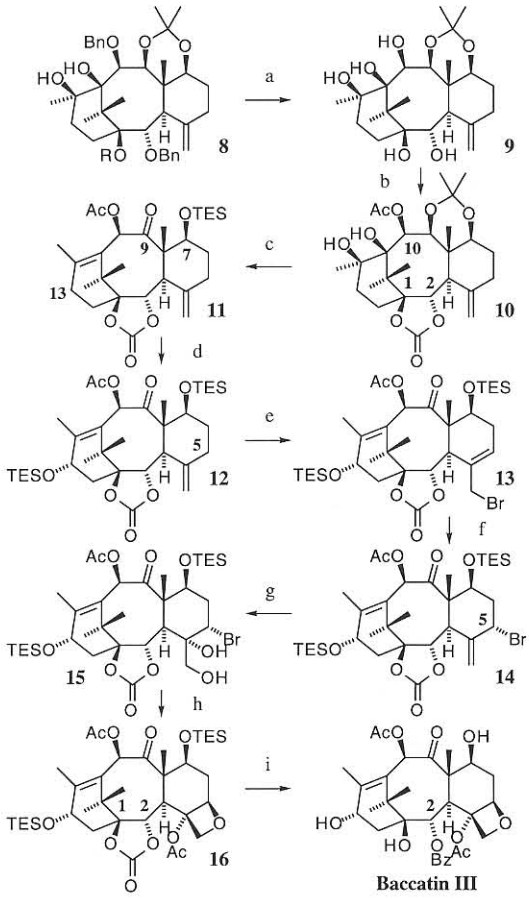


Figure 1.

Successive regioselective protection of the pentaol **9** with bis(trichloromethyl)carbonate and with acetic anhydride afforded the corresponding C-10 acetoxy, C-1, C-2 carbonate **10** in good yield. Deprotection of the acetonide function and regioselective protection of thus formed tetraol, followed by oxidation of triol with a combination of TPAP and NMO yielded C-9 ketone. A novel taxoid **11** was formed from the above ketone *via* the desulfurization of the intermediate thionocarbonate with trimethylphosphite. Regioselective oxygenation at the C-13 position of **11** with PCC and NaOAc gave an enone, which in turn was reduced to the desired α-alcohol stereoselectively on treatment with K-Selectride. On the other hand, reduction of the enone with other reducing reagents such as $NaBH_4$ and AlH_3 gave undesired β-alcohol as a major product. Protection of thus formed α-alcohol afforded tetracyclic compound **12** possessing all the functionalities necessary for the synthesis of baccatin III and Taxol. Since an effective method for the synthesis of baccatin III from the taxoid **12** had already been reported from our laboratory,[4] construction of oxetane ring onto the ABC ring system was followed by the reported procedure. Allylic bromination at the C-5 position of **12** using excess amounts of CuBr and $PhCO_3t$-Bu (1:1 molar ratio) gave separable allylic bromides **13** and **14** in 62% and 15% yields, respectively. Further, on treating the allylic bromide **13** with CuBr in CH_3CN at 55 °C, 25% of **13** and 64% of **14** were obtained because there existed an equilibrium between **13** and **14** under the thermodynamic conditions. MM2 conformational search, PM3 molecular orbital calculation and ^1H NMR experiment suggested that the most stable conformer of **14** was that as described in Figure 1. It is interesting to note that allylic bromide **14** having axial bromine at C-5 is more stable than its epimer having equatorial bromine at C-5. Since C ring of **14** has a chair form as shown in Figure 1, α-face selective dihydroxylation of **14** with OsO_4 proceeded smoothly to give a dihydroxy bromide **15** in 92% yield as a single stereoisomer. The desired oxetanol was obtained in good yield when this dihydroxy bromide **15** was treated with DBU at 50 °C in toluene. The corresponding acetate **16** was prepared by acetylation of the tertiary alcohol using acetic anhydride in pyridine. Finally, benzoylation at the C-2 position of C-1, C-2 carbonate **16**, followed by desilylation of the benzoate with HF·Py afforded baccatin III in high yield.



a) Na, liq. NH_3, -78 °C to -45 °C; TBAF, rt (100% from **8a**, 83% from **8b**, 61% from **8c**); b) $(CCl_3O)_2CO$, pyridine, CH_2Cl_2, -45 °C (100%); Ac_2O, DMAP, benzene, 35 °C (84%); c) 3N HCl, THF, 60 °C; TESCl, pyridine, rt (83% from **10**); TPAP, NMO, MS4Å, CH_2Cl_2, rt (76%); TCDI, DMAP, toluene, 100 °C (86%); $P(OMe)_3$, 110 °C (63%); d) PCC, NaOAc, celite, benzene, 95 °C (78%); K-Selectride, THF, -23 °C (87%); TESOTf, pyridine, -23 °C (98%); e) CuBr, $PhCO_3t$-Bu, CH_3CN, -23 °C (62% of **13**, 15% of **14**); f) CuBr, CH_3CN, 55 °C (25% of **13**, 64% of **14**); g) OsO_4, pyridine, THF, rt (92%); h) DBU, pyridine, toluene, 50 °C (77% based on 52% conversion); Ac_2O, pyridine, DMAP, rt (91%); i) PhLi, THF, -78 °C (94%); HF·Py, THF, rt (96%)

Scheme 3.

Thus, a new method for the synthesis of baccatin III, ABCD ring system of Taxol, from the optically active BC ring system *via* intramolecular pinacol coupling, an introduction of C-13 hydroxyl group and oxetane formation reaction has been established.

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References and Notes

1 I. Shiina, H. Iwadare, H. Sakoh, Y. Tani, M. Hasegawa, K. Saitoh, and T. Mukaiyama, *Chem. Lett.* **1997**, 1139; references cited therein. For total synthesis of Taxol by the groups of Holton, Nicolaou, Danishefsky, and Wender, see references in this previous paper.

2 We observed that low-valent titanium reagent prepared from $TiCl_2$ and $LiAlH_4$ has more activity compared with that of reagent prepared from $TiCl_3$ or $TiCl_4$ and $LiAlH_4$ for this reaction. See, T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, **1973**, 1041; A. Ishida and T. Mukaiyama, *Chem. Lett.*, **1976**, 1127. Recent review: A. Fürstner and B. Bogdanovic, *Angew. Chem., Int. Ed. Engl.*, **35**, 2442 (1996).

3 **9** (100% ee); $[\alpha]_D^{28}$ -4.0° (c 0.489, MeOH).

4 I. Shiina, M. Saitoh, K. Nishimura, K. Saitoh, and T. Mukaiyama, *Chem. Lett.*, **1996**, 223.