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Total Synthesis of Koninginin A and Its Diastereoisomer

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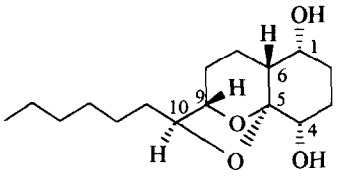
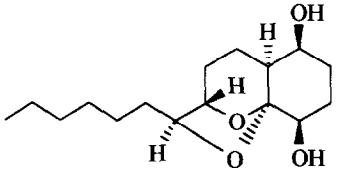
Abstract: A total synthesis of Koninginin A and its diastereoisomer starting from L-(+) tartaric acid is described. The key steps involved the Pd catalyzed cross-coupling of alkylboron with vinyl triflate and the $^1O_2$ addition to diene. This study not only corrected the relative configuration of Koninginin A, but also assigned its absolute configuration as 1S, 4R, 5S, 6S, 9S, 10S.

In recent years considerable interest has been shown in the use of *Trichoderma* spp. as biological control agents. Koninginin A, isolated by R. H. Cox[1] and E. Ghisalberti[2] from the cultures of *Trichoderma harzianum* and *Trichoderma koningii* Oudem., exhibits substantial antibiotic activity towards the take-all fungus, *Gaeumannomyces graminis var. tritici*, as well as inhibits the growth of etiolated coleoptiles. Its relative stereochemistry was assigned by E. Ghisalberti as shown in **1a**. However, his deduction for the assignment was doubtful, especially for eliminating the possibility of structure **1b**. Recently, K. Mori has reported the total synthesis of (±) Koninginin A.[3] Unfortunately, the same problem of stereochemistry could not be solved in his route. Because of the failure of preparing a single crystal for X-ray diffraction,[2] it is essential to develop an efficient synthetic route to prepare both **1a** and **1b**, which are amenable to the assignment of its absolute configuration. Herein, we communicate our results.



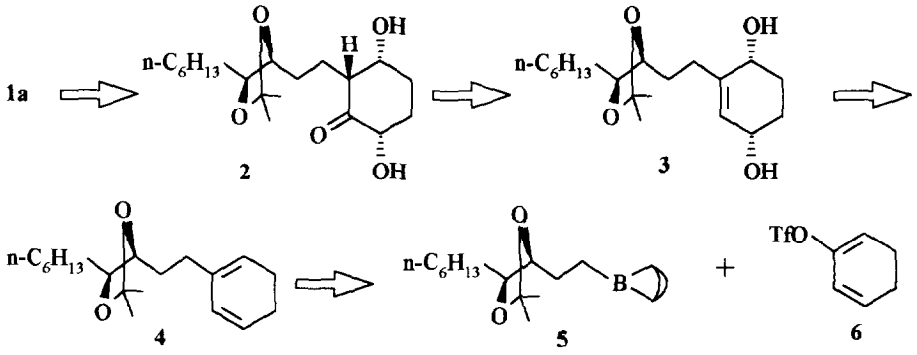
1a



1b

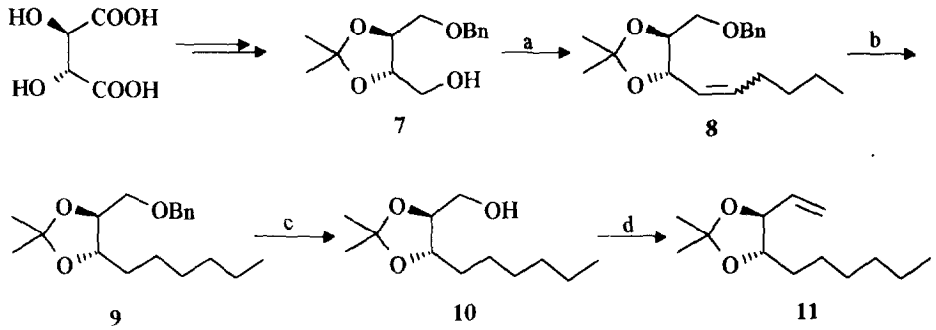
Our retrosynthetic analysis is outlined in **Scheme 1**. After functional group transformation, it was envisioned that the 1,4-*syn*-dihydroxyl group in **3** could be elaborated by the non-stereoselective $^1O_2$ addition to diene **4**. Accordingly, attention was directed towards the regioselective connection of the side chain with a cyclohexene moiety to form the key intermediate **4**. In this strategy, we felt that the most efficient approach would be the Pd catalyzed Suzuki reaction of the alkylboron **5** with vinyl triflate **6**,[4] which gave exclusively desired coupling product.

The synthesis of side chain **5** was started from natural L-(+) tartaric acid (**Scheme 2**), which was converted to compound **7** in four steps following the known procedure.[5] Swern oxidation of **7** followed by



Scheme 1

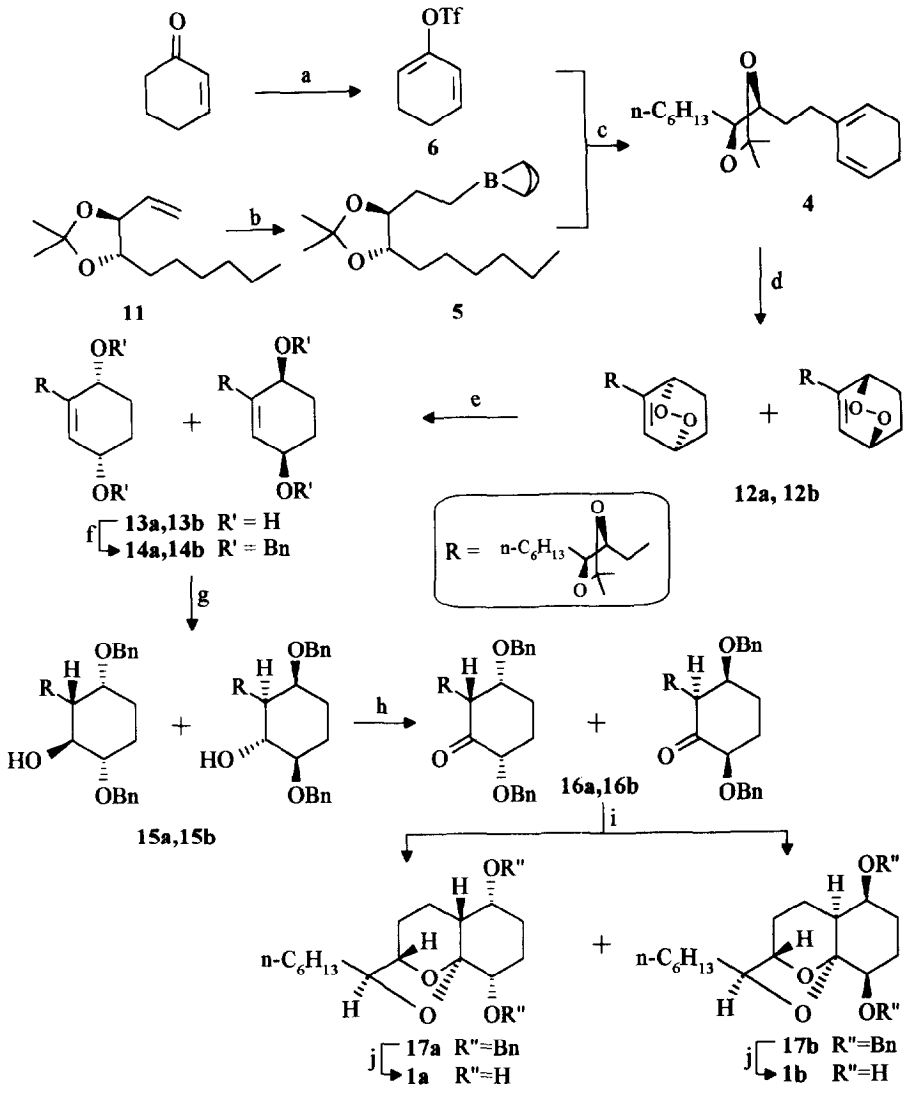
Wittig reaction afforded **8** in 70% yield. Attempt to transform **8** on Pd-C to **10** in one step failed. **8** was then subjected to an alternative approach: the double bond was first hydrogenated over Raney Ni, then the benzyl group was removed by Li/liq. NH_3. The yield of **10** still reached 93% in the above 2 steps. Another side chain was lengthened by one carbon atom via additional Swern oxidation and Wittig reaction. Therefore, we accomplished the side chain in 10 steps with 30% overall yield.



Scheme 2. *Reagents and Conditions*: a. 1) $(COCl)_2$, DMSO, Et_3N, -78°C, 2) $(n\text{-}C_5H_{11})PPh_3Br$, n-BuLi, THF, -50°C→r.t., 70%; b. Raney Ni, H_2, EtOH, r.t., 95%; c. Li, Liq. NH_3, -30°C, 97%; d. 1) $(COCl)_2$, DMSO, Et_3N, -78°C, 2) Ph_3PMeI, t-BuOK, benzene, r.t., 83%.

According to the procedure of Suzuki[4] , the regioselective formation of **4** successfully proceeded by the Pd catalyzed cross-coupling reaction of alkylboron **5**, formed *in situ* by treatment of **11** with 9-BBN in THF, with triflate **6**, which was generated by treatment of 2-cyclohexenone with LDA/Tf_2NPh.[6] $^1O_2$ addition of **4** and subsequent reduction of the resulting peroxide with $LiAlH_4$ led to the mixture of two diastereoisomers **13a** and **13b** in a 1:1 ratio, which was not separable by chromatography(**Scheme 3**).

After protection of the two hydroxyl groups of **13a**, **13b** as benzyl ether, we explored the conversion of double bond to carbonyl group. The optimal procedure was stereoselective hydroboration[7] followed by Swern oxidation. When **14** was treated with BH_3· THF solution at -78°C then slowly raised to r.t., a mixture of hydroxyl compounds obtained in 71% yield. Albeit still inseparable, their stereochemistry, as depicted in **15a**, **15b**, could be assigned by the reaction mechanism. Swern oxidation of **15** afforded **16** in 74% yield, which upon treatment with amberlyst-15 at 30°C in wet CH_2Cl_2 provided the separable tricyclic ketals **17a** and **17b**, with 73% conversion rate, and in 93% total yield (excluding the recovered **16a** and **16b**). The ratio of **17a**



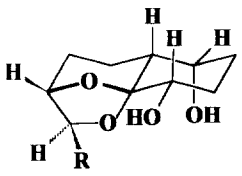
Scheme 3. *Reagents and Conditions*: a. LDA, DME, -78°C then Tf_2NPh, 0°C, 63%; b. 9-BBN, THF, 0°C→r.t. c. $K_3PO_4 \cdot 3H_2O$, $Pd(PPh_3)_4$, dioxane, 85°C, 61%; d. $^1O_2$, Rose Bengel, MeOH, 0°C, 62%; e. $LiAlH_4$, Et_2O, 0°C, 87%; f. PhCOCl, Et_3N, DMAP, r.t., 76%; g. 1) BH_3, THF, -78°C→r.t., 2) 30% H_2O_2, 3M NaOH, 71%; h. $(COCl)_2$, DMSO, Et_3N, -78°C, 74%; i. amberlyst-15, CH_2Cl_2, 30°C, 93% total yield; j. H_2,, Pd-C, EtOH, r.t., 92%.

to **17b** was 1:1. Hydrogenolysis of **17a** and **17b** with Pd-C gave the target compounds **1a**[8] and **1b** respectively. Compound **1b** was identical with the natural Koninginin A in all respects except for a bit higher melting point and optical rotation.[9]

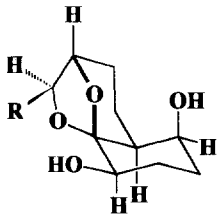
With the sample of **1a** and **1b** in hand,extensive NMR study provided a solution to their stereochemistry. It is worthwhile to note that the splitting pattern of 6-H(see ref.8 and 9) showed the presence of an axial-axial coupling between 6-H and 7-H in **1a** and indicated a trans-fused conformation.(**scheme 4**) Further evidences for this assignment were obtained by the application of Mosher's method.[10] Thus, the absolute configuration of

Koninginin A should be assigned as 1S, 4R, 5S, 6S, 9S, 10S, as shown in **1b.** these results will be discussed in detail elsewhere.

Scheme 4



1a



1b

Acknowledgment:

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References and Notes:

1. Cutler, H. G.; Himmelsbach, D. S.; Arrendale, R. F.; Cole, P. D. and Cox, R. H.*Agric. Biol. Chem.* **1989**, 53, 2605-2611.
2. Almassi, F.; Ghisalberti, E. L.; Narbey, M. J. *Journal of Natural Products*, **1991**, 54, 396-402.
3. Mori, K. and Abe, K. *Polish J. Chem.* **1994**, 68, 2255-2263.
4. Oh-e, T.; Miyaura, N. and Suzuki, A. *J. Org. Chem.* **1993**, 58, 2201-2208.
5. Hungerbuhler, E.; Seebuch, D. *Helv. Chim. Acta* **1981**, 64, 687.
6. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 24, 979-982.
7. a. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E. and Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, 112, 5583. b. Pingliand, L.; Vandewalle, M. *Synlett* **1994**, 228.
8. **1a,** a colorless oil, shows the following data: $\alpha]_D^{20}$ -45.1^O (C 1.03, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δppm: 4.19(1H, m, 9-H), 4.10(1H, t, J=7.0 Hz, 10-H), 3.66(1H, dd, J=5.1,12.4Hz, 4-H), 3.62(1H, m, 1-H), 2.10(1H, dddd, J=6.0, 11.5, 13.3, 13.3 Hz, 7-H_A), 1.98(1H, dddd, J=3.2, 5.8, 13.3, 13.3 Hz, 8-H_A), 1.94(1H, m, 3-H_B), 1.91(1H, m, 2-H_B), 1.76(1H, dddd, J=2.9, 12.4, 13.1,13.1 Hz, 3-H_A), 1.70(1H, ddd, J=3.0, 5.8, 11.5 Hz, 6-H), 1.65-1.55(3H, m, 8-H_B ,7-H_B , 11-H), 1.50-1.45(2H, m, 2-H_A , 11-H), 1.40-1.25(8H, m, 12~15-H), 0.89(3H, t, J=7.0Hz, 16-H). ^{13}C NMR (150 MHz, $CDCl_3$) δppm: 109.2(5-C), 79.9(10-C), 77.9(9-C), 69.1(4-C), 67.0(1-C), 42.6(6-C), 35.0(11-C), 31.6(14-C), 30.8(2-C), 29.0(13-C), 27.7(8-C), 26.3(3-C), 25.5(12-C), 22.5(15-C), 18.4(7-C), 14.0(16-C).
9. **1b,** $\alpha]_D^{20}$-26.3^O (C 0.89, $CHCl_3$) { lit.[2]: -20^O (C 0.7, $CHCl_3$)}, m.p. 89.8-90.5^{O}C { lit: 77-79^{O}C[2], or 80-84^{O}C[1]}.^{1}H NMR (600 MHz, $CDCl_3$) δppm: 4.32(1H, m, 9-H), 4.03(1H, t, J=7.0 Hz, 10-H), 3.89(1H, dd,J=2.9,11.0Hz, 1-H), 3.61(1H, dd, J=4.8, 11.8Hz, 4-H), 3.15(1H, d, J=11.0Hz, 1-OH), 2.27(1H, dddd, J=3.8, 6.5, 13.3, 13.3 Hz, 8-H_A), 2.10(1H, m,7-H_A), 1.96(1H, m, 3-H_B), 1.87(1H, m, 2-H_B), 1.82(1H, dddd, J=3.9, 11.8, 13.0,13.0 Hz, 3-H_A), 1.72(1H, dd, J=6.5, 13.9 Hz, 7-H_B),1.58(1H, dd, J=2.9,7.3Hz, 6-H) 1.60-1.57(1H, m, 11-H), 1.54-1.47(3H, m, 2-H_A , 11-H, 8-H_B), 1.41-1.26(8H, m, 12~15H),0.88(3H,t,J=7.0Hz, 16-H).
10. Ohtani, I.; Kusumi, T.; Kashman, Y. and Kakisawa, H., *J. Am. Chem. Soc.* **1991**,113,4092

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