Asian Journal of Chemistry; Vol. 24, No. 3 (2012), 1411-1412

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

Total Synthesis of Harringtonolide-Introducing Antidihydroxy Group and Forming the Lactone

WEILI LI

Department of Chemistry, Kunming University, No.2, Puxin Road, Kunming High and New Tech Development Zone, Kunming 650214, Yunnan, P.R. China

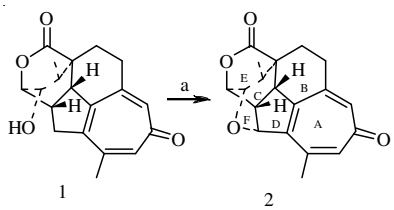
Corresponding author: Tel: +86 871 5098476; E-mail: lierkm@163.com

(*Received*: 21 April 2011; *Accepted*: 14 November 2011) AJC-10676

We reported a new relative stereochemical studies on the total synthesis of harringtonolide where the strategy relied upon the application of intermolecular Diels-Alder reaction (IMDA) to form the tricyclic skeleton proceeded very efficiently as we expected. Reductive-oxidation of the enolate was carried out with borane followed by hydrogen peroxide to give the desired crucial anti dihydroxy derivative. With the critical precursor in hand, the lactone was formed.

Key Words: Harringtonolide, Reduction-oxidation, Lactone.

Harringtonolide (**2**), which is the natural diterpenoid tropone[1], have a characteristic hexacyclic skeleton possessing seven asymmetric centers and was firstly isolated from Cephalotaxus harringtonia in north America in 1978. At about the same time, harringtonolide was independently discovered in the bark of related Chinese species Cephalotaxus Hainanensis Li under the name hainanolide[2]. The structure was determined by X-ray diffraction and demonstrated antitumor and antiviral activities in preliminary test[3,4]. In *C. hainanensis*, **2** was accompanied by the closely related, but biologically inactive carbinol, hainanolidol **1**, the structure of which was established by conversion into **2** by transannular oxidation with lead tetraacetate (Fig. 1)[5]. To explore the chemistry and therapeutic potential of these unusual compounds, the total synthesis of this diterpenoid tropone has been reported. The total synthesis of harringtonolide was first achieved *via* a Mukaiyama-like aldol process in a key tropone forming step by Mander and co-workers[6] and a different scheme of its synthesis has been studied in Chinese laboratories[7-11].



1 2

Fig. 1. Structure of Harringtonolide; reagents and conditions: a, $Pb(OAc)_4$, *hv*.

The synthesis of tricyclic ketone **9** was reported by Yang *et al.*[7]. The synthetic route of the key intermediate **15** from ketone **9** was shown in Fig. 2. After a detailed survey of the previous results, we chose ketone **9** as a starting material, which was selective hydrolyzed by heating with barium hydroxide in $MeOH/H_2O$ to afford the corresponding acid **10**. Treatment of compound **10** in boiling xylene to decarboxylate the carboxyl group at C_1 formed the compound **11** in 81 % yield along with another isomer in 5 % yield. NOE revealed that C_1-H and C_{8b}-H of compound **11** at the same side. Followed by hydrogenation with palladium on carbon afforded the compound **12** quantificationally. The stereochemistry of H-2a was determined by the NOE spectra. Irradiation of H-8b caused enhancements of signals of both H-2a and H-8b in compound **12** and revealed that C_{2a}-H and C_{8a}-H at the same side. Ketone **12** was kinetically enolized[12] and the enolate was trapped with MOMCl in THF at -78 ºC to afford the compound **13** in 70 % yield. Comparing its IR spectrum with that of ketone **13** the enolate showed the absence of C=O band at 1707 cm^{-1} and instead appearance of a new band at 1666 cm^{-1} for C=C. The ^1H NMR spectrum showed the =CH- signal at δ 4.70 ppm, a doublet for C_5-Me at δ 0.90 ppm and signals for C_4-OCH_2OCH_3 at δ 4.93 ppm (d, 1H, J = 7 Hz) and δ 4.91 ppm (d, 1H, J = 7 Hz) and δ 3.40 ppm (s, 3H). The IR and NMR spectra coincide nicely with the structure of compound **13**. Reductive-oxidation[13] of compound **13** was carried out with borane followed by H_2O_2 to give compound **14** as crystalline solid (m.p. 119.8-120.4 ºC) in 64 % yield. HMBC and HMQC spectra identified the skeleton and H, C correlation of compound **14**. No double bond signals were observed in its ^1H NMR spectrum. Signals at δ 3.86 ppm (dd, 1H, J = 6 Hz, 12 Hz) and δ 3.20 ppm (d,

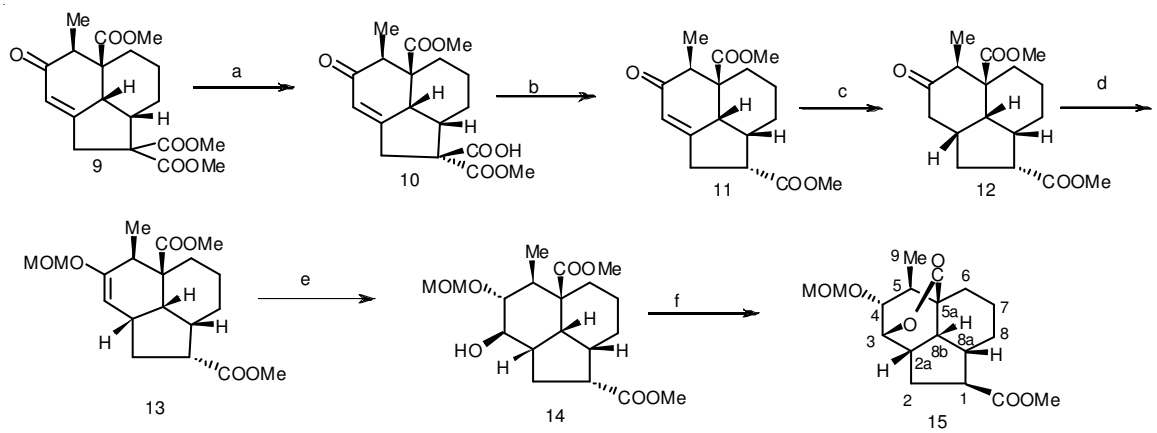


Fig. 2. Reagents and conditions: (a) $Ba(OH)_2$, $MeOH/H_2O$, 50 ºC, 83 %; (b) Xylene, refluxed, 81 %; (c) Pd/C, H_2, EtOH, rt; (d) MOMCl, LICA/THF, -78 ºC, 72 %; (e) BH_3-H_2O_2, THF, 0 ºC, 64 %; (f) NaH, THF, 86 %.

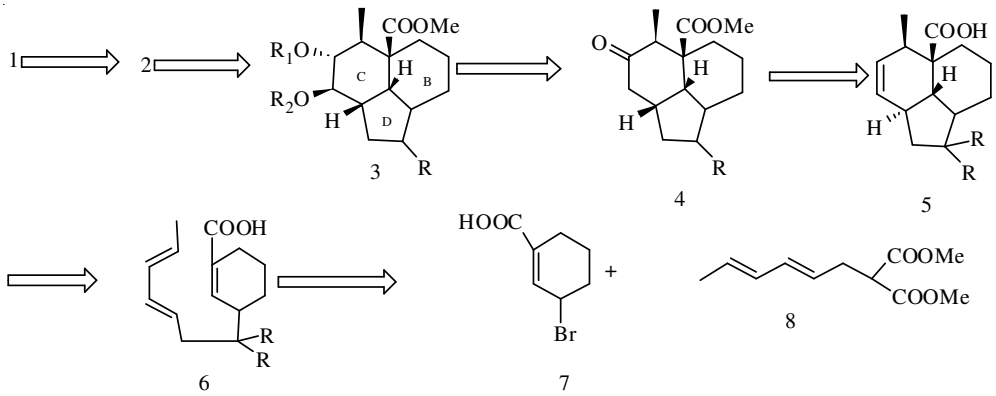


Fig. 3. Retrosynthestic analysis of **2**.

1H, J = 6 Hz) were assigned to C_3-H and C_4-H respectively. NOE revealed that A, B, C three rings being *cis* fused as that in hainanolide and with 5a-$COOCH_3$ and C_3-OH at the same side as H_{2a} and C_4-OCH_2OCH_3 at back side being at the right positions for building lactone ring and oxobridge. Treatment of compound **14** with a base of NaH in THF to proceed ring close between of the C_3-OH and C_{5a}-COOMe formed ring D to afford compound 15 in 86 % yield. Two absorption bands of -COO- showed at 1734 cm^{-1} and 1759 cm^{-1} in IR spectra of compound **15**. The latter band (1759 cm^{-1}) was assigned to δ-lactone carbonyl. This was supported by the reported lactone absorption in the IR spectrum of hainanolidol[2] at wavelength of 1760 cm^{-1}. The band at 1736 cm^{-1} is related to the ester methyl group at C_1 and only one ester methyl group was found in the ^1H NMR spectrum of compound **15**. This demonstrated that the lactonization has taken place under the reaction condition as expected. The stereochemistry of H-1 was determined by the NOE spectra. Irradiation of H-1 caused enhancements of signals of both H-2α and H-5 in compound **15**. All the above results indicated that H-1 in compound **15** is at α position.

Herein a new related stereochemical studies on the total synthesis of harringtonolide (**2**) is reported, where the strategy relied upon the application of intermolecular Diels-Alder reaction (IMDA) as shown in Fig. 3. Retrosynthetic analysis of **2** revealed that the lactone E and ether ring F would be constructed through application of an intermolecular ester exchanger and 1,4-nucleophilic addition reaction from anti dihydroxy compound **3**. The anti dihydroxy **3** would come through the reductive-oxidation of the enolate derived from ketone **4** with borane reagent. Ketone **4** would be derived through reduction of the α,β-unsaturated ketone intermediate come from oxidation of olefin **5**. We anticipated that the critical tricyclic skeleton **5** would be efficiently constructed through the application intermolecular Diels-Alder reaction of triene **6**. The intermediate would be given through the substitution reaction with diene **8** and dienophilic **7**.

Conclusion

In conclusion, we achieved the key intermediate for the total synthesis of harringtonolide through the enolate by enolation followed by reductive-oxidation to introduce C_3-β-OH and C_4-α-OH and form the lactone.

REFERENCES

1. J.G. Buta, J.L. Flippen and W.R. Lusby, *J. Org. Chem.*, **49**, 1002 (1978).
2. N. Sun, Z. Xue and L. Liang, *Acta Pharm. Sin.*, **14**, 39 (1979).
3. S. Kang, S. Cai and L. Teng, *Acta Pharm. Sin.*, **16**, 867 (1981).
4. X. Xue, N. Sun and X. Liang, *Acta Pharm. Sin.*, **17**, 236 (1982).
5. N. Sun, Z. Xue, X. Liang and L. Huang, *Acta Pharm. Sin.*, **16**, 233 (1981).
6. B. Frey, A.P. Wells, D.H. Regers and L.N. Mander, *J. Am. Chem. Soc.*, **120**, 1914 (1998).
7. Z.Q. Yang, S.Z. Chen and L. Huang, *Chin. Chem. Lett.*, **9**, 281 (1998).
8. L.Y. Zhang, W.Q. Yang, S.Z. Chen and L. Huang, *Chin. Chem. Lett.*, **8**, 15 (1997).
9. W.Q. Yang, S.Z. Chen and L. Huang, *Chin. Chem. Lett.*, **8**, 1043 (1997).
10. X.M. Yu, S.Z. Chen and L. Huang, *Chin. Chem. Lett.*, **11**, 295 (2000).
11. Y.W. Li, L.Y. Zhu and L. Huang, *Chin. Chem. Lett.*, **15**, 397 (2004).
12. I. Fleming and I. Paterson, *Synthesis*, 736 (1979).
13. H.C. Brown and R.L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968).