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First enantioselective synthesis of manoalide: application of aldehyde–dioxinone enantioselective condensation

Annunziata Soriente, Margherita De Rosa, Aniello Apicella, Arrigo Scettri * and Guido Sodano *

Dipartimento di Chimica, Università di Salerno, 84081 Baronissi (SA), Italy

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Abstract

Manoalide, an analgesic and anti-inflammatory sesterterpene, has been stereoselectively synthesized for the first time. The C-4 stereogenic centre has been introduced in an early step by enantioselective aldol condensation using a Ti(O*i*Pr)$_4$/(*R*)-(+)-binol complex.

Manoalide **1**, a sesterterpene isolated from a marine sponge,[1] is a potent analgesic and anti-inflammatory agent,[2] whose mechanism of action involves inhibition of phospholipase A_2 (PLA_2). Because of its peculiar pharmacological activities, manoalide has become an interesting synthetic target, leading to seven syntheses reported to date.[3] Since the reported syntheses of manoalide afford only racemic material, we have devised a synthetic approach leading to the first asymmetric synthesis of manoalide.

Manoalide has three stereogenic centres (C-4, C-24 and C-25), only one of them being fixed (C-4). In fact, the other two centres (C-24 and C-25) are hemiacetal carbons and thus, subject to epimerization in solution. Therefore the problem of the stereocontrol in the synthesis of manoalide is reduced to the control of the stereochemistry at C-4. Our strategy (Scheme 1) was essentially based on the synthesis of the two fragments **2** and **3**, the former being destined to become the polyisoprenic side chain of **1** and the latter representing the chiral precursor of the pyranofuranone system of manoalide. The two fragments could be assembled through alkylation of the 1,3-dicarbonyl moiety of **3**.

Alkyl bromide **2a** was prepared from β-ionone by Hoffmann's procedure.[3f] However, an improvement in the yields of the first step of the reported synthesis was achieved by selective reduction of β-ionone via hydrosilylation as indicated by Ojima and Kogure.[4] Compound **2a** was obtained as a 9:1 *E*:*Z* mixture in 45% total yield and was quantitatively converted into the corresponding iodide **2b** by treatment with NaI in refluxing acetone.

* Corresponding authors. E-mail: sodano@dia.unisa.it

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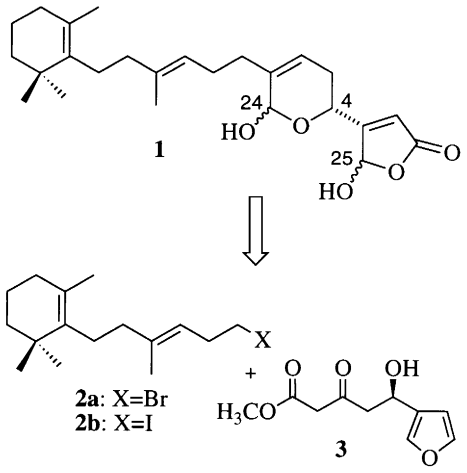
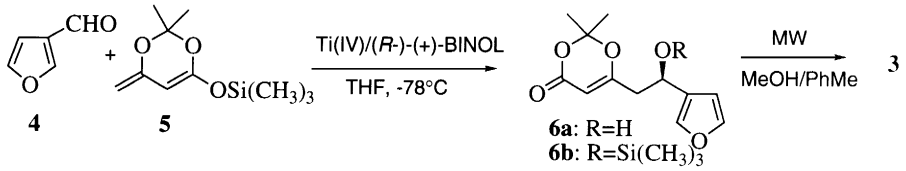


Scheme 1.

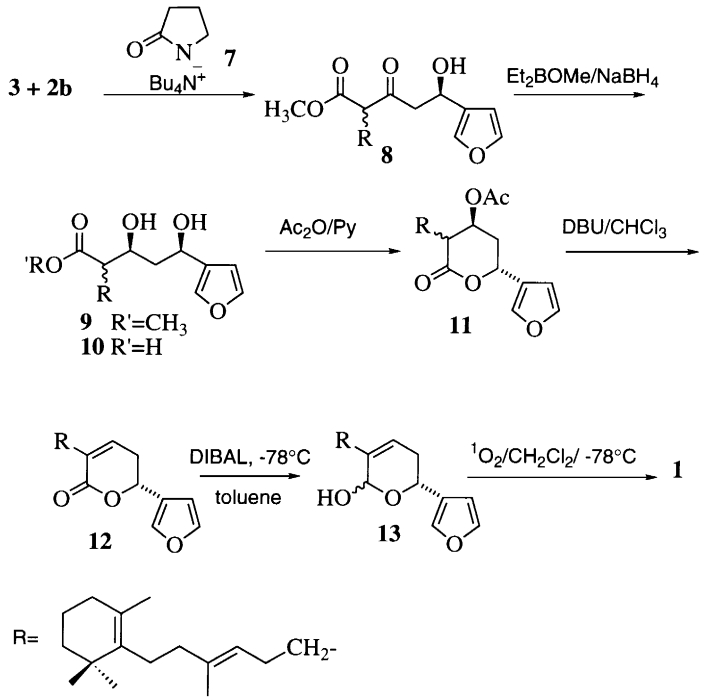
The second subunit **3** bearing the stereogenic centre with the desired *R* configuration was prepared according to the two step sequence depicted in Scheme 2. The stereogenic centre at C-4 was introduced by exploitation of an aldehyde–dioxinone enantioselective condensation recently utilized for the preparation of chiral non-racemic 6-(furan-3-yl)-5,6-dihydro-pyran-2-ones.[5] This approach consists of a titanium catalyzed aldol reaction, based upon a modification of the methodology of Sato.[6] Carreira's methodology, involving enantioselective aldol condensation of silyloxydienes of type **5** in the presence of chiral Ti(IV)[7] or Cu(II)[8] catalysts, seemed particularly attractive both for its efficiency and high degree of enantioselectivity leading to silylated aldols of type **6b**. However, we have found that the reported acidic work-up[8] of **6b** for the regeneration of the alcoholic function resulted in partial racemization. For this reason, we used Sato's procedure,[6] based on the condensation of the silyloxydiene **5** with 3-formyl furan **4** in the presence of Ti(O*i*Pr)$_4$/(*R*)-(+)-binol complex for the synthesis of the aldol **6a**.[5] We have now found that using 0.5 equiv. (instead of 0.17 equiv. used in the original procedure) of Ti(O*i*Pr)$_4$/(*R*)-(+)-binol complex leads to an improvement both of yields and of e.e., leading to **6a** in 65% yield and with an 87% e.e. (^{1}H NMR analysis on the corresponding (*S*)-MTPA ester). The subsequent conversion of **6a** into the key intermediate **3** was performed in a very efficient way (>90%) by microwave (MW) irradiation of a MeOH/PhMe solution of **6a**.



Scheme 2.

Alkylation of **3** with the iodide **2b** proved difficult under various conditions. In fact, very carefully controlled experimental conditions had to be used in order to limit the occurrence of undesired competitive side processes. Monoalkylation of **3** (Scheme 3) was eventually obtained in satisfactory yield by using the tetrabutylammonium salt of 2-pyrrolidone anion **7** as a phase transfer catalyst, prepared by chemical methods as previously described by Shono et al.[9] The crude alkylation product **8** was reduced with Et$_2$BOMe/NaBH$_4$ according to Prasad methodology[10] to afford the diol **9** in 31% overall yield from **3**. The remaining part of the synthesis followed our previous methodology set up for the synthesis of manoalide and cacospongionolide analogues.[11,12] Thus, **9** was submitted to a three step sequence

including hydrolysis to the acid **10**, acetylation and simultaneous cyclization to **11** and finally, elimination with DBU to afford the lactone **12** in 30% overall yield from **9**. Reduction of **12** with DIBAL afforded the unstable lactol **13** which was quickly photooxygenated to afford manoalide **1** in 35% yield from **12**. Synthetic **1** has $[\alpha]_D$ +65 (c=0.2; MeOH) while for the natural product an $[\alpha]_D$ +80 (c=0.2; MeOH) was reported,[13] suggesting an 81% e.e. for the synthetic manoalide which compares well with the 87% e.e. of the starting chiral material **6a**.



Scheme 3.

Acknowledgements

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References

1. De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611.
2. For reviews, see: (a) Mayer, A. M. S.; Jacobs, R. S. In *Biomedical Importance of Marine Organisms*; Fautin, D. G., Ed.; California Academy of Sciences: San Francisco, 1988; pp. 133–142; (b) Potts, B. C. M.; Faulkner, D. J.; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55*, 1701; (c) Mann, J. *Nature* **1992**, *358*, 540; (d) Soriente, A.; De Rosa, M.; Scettri, A.; Sodano, G.; Terencio, M. C.; Paya, M.; Alcaraz, M. J. *Curr. Med. Chem*. **1999**, *6*, 415–431.
3. (a) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827; (b) Garst, M. E.; Tallman, E. A.; Bonfiglio, J. N.; Harcourt, D.; Ljungwe, E. B.; Tran, A. *Tetrahedron Lett.* **1986**, *27*, 4533; (c) Katsumura, J.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1988**, *29*, 1173; (d) Bury, P.; Hareau, G.; Kocienski, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793; (e)

Pommier, A.; Kocienski, P. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1139; (f) Coombs, J.; Lattmann, E.; Hoffmann, H. M. R. *Synthesis* **1998**, 1367.
4. Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.
5. Soriente, A.; De Rosa, M.; Dovinola, P.; Sodano, G.; Scettri A. *Tetrahedron: Asymmetry* **1998**, *9*, 2197.
6. Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435.
7. Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360.
8. Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
9. Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907.
10. Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
11. Soriente, A.; De Rosa, M.; Scettri, A.; Sodano, G. *Tetrahedron Lett.* **1996**, *37*, 8007.
12. De Rosa, M.; Giordano, S.; Scettri, A.; Sodano, G.; Soriente, A.; Garcia Pastor, P.; Alcaraz, M. J.; Paya, M. *J. Med. Chem.* **1998**, *41*, 3232.
13. Kobayashi, M.; Okamoto, T.; Hayashi, K.; Yokoyama, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 265.