Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7771-7774, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01717-4

Intramolecular Coupling Reaction Promoted by SmI_2 in a Synthetic Approach of Forskolin.

Claude Anies, Ange Pancrazi,* Jean-Yves Lallemand.

Laboratoire de Synthèse Organique associé au C.N.R.S., DCSO, Ecole Polytechnique, 91128, Palaiseau, France.

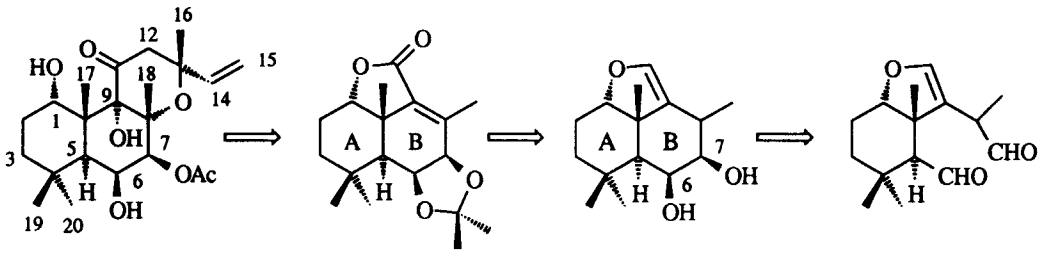
Thierry Prangé

Laboratoire de Chimie Structurale Biomoléculaire, Université Paris Nord, 74 rue Marcel Cachin, 93012 Bobigny France.

Key Words *: Radical cyclisations , Bu_3SnH, SmI_2, pinacolic coupling reaction, Dess-Martin oxidation, forskolin.*

Abstract *: From available hydroxy-aldehyde **6**, propargylic derivative **8** was prepared and treated with Bu_3SnH to give in 95% yield the bicyclic vinyl stannane **10**. After **10** was converted into the diol **15**, this latter was oxidized with the Dess-Martin reagent into the dialdehyde **4**. Compound **4** was then submitted to a pinacolic coupling reaction leading to the bicyclic cis-diol **3** in a stereospecific manner.*

Forskolin **1**, a labdane diterpene isolated from the roots of the Indian plant *Coleus Forskohlii* ,[1] has been shown to activate adenylate cyclases,[2] to inhibit platelet aggregation *in vitro* and *in vivo*, and to present therapeutic potential toward bronchial asthma,[3] congestive heart failure [4] and glaucoma.[5]



1 **Forskolin** **2** **3** **4**

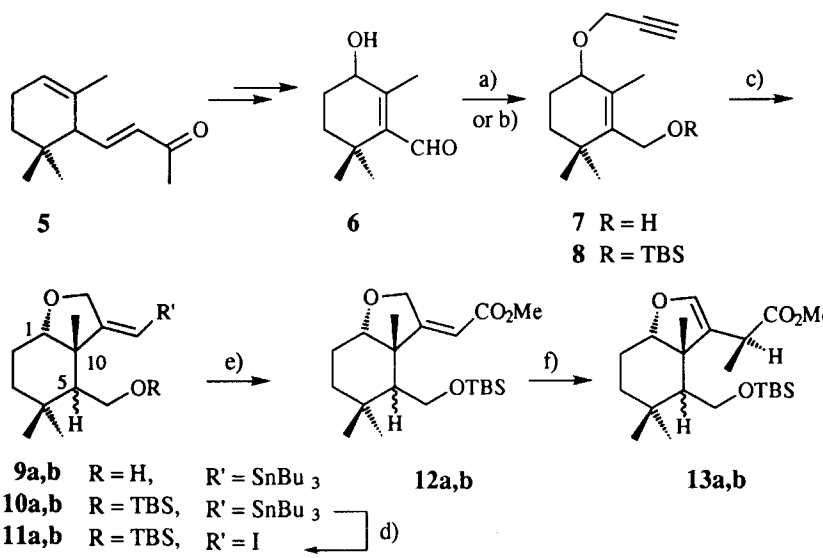
Owing to its complex polyoxygenated tricyclic structure and potent biological activities, Forskolin **1** still represents a synthetic challenge for organic chemists.[6-8] Various strategies appeared to be highly convenient for the construction of the bicyclic A-B system, as already reported in the total synthesis of **1**,[7] and synthetic

approaches.[6-8] One of the challenges in a synthesis of forskolin is to solve the difficult problem of establishing the 6β,7β diol in an efficient and highly stereoselective reaction.

After developing a promising route to forskolin *via* a tandem Michael-Claisen reaction,[9] we also studied another approach involving radical cyclisation which could be advantageously carried out on non protected derivatives, *the main goal in this new approach being the closure of the B ring with the concomitant cis-6β,7β-diol formation.*

A convenient preparation of the lactone **2**, common intermediate to the three previously achieved total synthesis of forskolin,[7] was therefore envisaged from diol **3**, using an SmI_2 pinacolic coupling reaction [10] performed on dialdehyde **4**.

The known hydroxy-aldehyde **6** [11] was prepared from commercial α-ionone **5**, and converted into propargylic derivatives **7** and **8** *via* classical reactions. A first radical cyclisation between the acetylenic and olefinic functions was obtained by treatment of **7** and **8** with Bu_3SnH, AIBN, in refluxing toluene for 2h,[12] to give in good yield the two epimeric vinyl-stannanes **9a,b** and **10a,b** respectively (>95% yield, **a/b** = 1:1). Purified separated isomers **9a** and **9b** were shown by ^1H and ^{13}C NMR analysis including NOE experiments to be the *trans* and *cis* C_5-C_{10} linked bicyclic products respectively and to present a *cis*- octahydrobenzofuran skeleton[13].



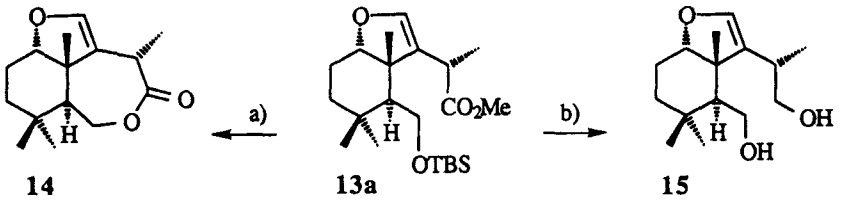
a) NaOH/H_2O 60% weight, Bu_4NI, cat, propargyl bromide, toluene, 20°C, 17h, 91%; $NaBH_4$, MeOH, 0°C, 1h, 75%, —> **7** (48% from **5**); b) $NaBH_4$, MeOH, 0°C, 1h, 75%; TBSCl, Im, DMF, 0°C, 4h, 63%; NaOH/H_2O 60% weight, Bu_4NI, cat, propargyl bromide, Tol, 20°C, 17h,—> **8** 96%. c) Bu_3SnH (1.7eq) 0.05M in Tol, AIBN 0.1%mol, reflux 2h, 95%. d) I_2, Et_2O, 20°C, 3h, >95%. e) **10a,b** BuLi, THF, -78°C, 1h, $ClCO_2Me$, 0°C-> 20°C, 2h, —> **12a,b**,85%. f) LDA-HMPT, THF, -78°C, MeI, -78°C—> 20°C, 95%.

In order to prepare the conjugated methyl esters **12a,b**, the iodo compounds **11a,b** were also prepared by an iodine exchange [14] from **10a,b**. At this time the best results were obtained, for the carboxylation step, by treating vinyl-stannanes **10a,b** with nBuLi, THF at -78°C, and quenching with $ClCO_2Me$ (85%yield).

Further methylation of the conjugated ester mixture **12a** and **12b** (LDA, THF, HMPA, MeI, -78°C) was regiospecific and gave only **13a** and **13b**; the convex conformations of the **12a** and **12b** isomers, due to

the *cis* ring junction of the octahydrobenzofuran system, could explain the high level of stereocontrol of the methylation step.

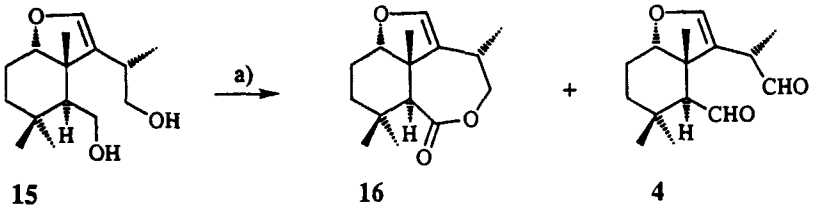
When separated isomer **13a** was treated under TBAF-THF conditions (to remove the TBS protecting group), lactone **14** was obtained quantitatively; alternatively, reduction of the ester function followed by removal of the TBS protecting group afforded the required diol **15** in 55% yield (**15** could be obtained also by $LiAlH_4$ reduction of lactone **14** in 85% yield).



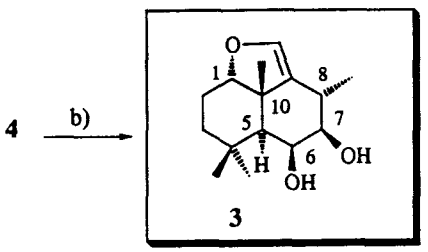
14 **13a** **15**

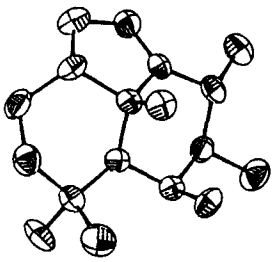
a) TBAF, THF, 20°C, 12h, 95%.; b) $LiAlH_4$, THF, 0°C, 1h, 80%; TBAF, THF, 20°C, 12h, 68%.

Attempts to oxidize diol **15** into the dialdehyde **4** using Swern conditions failed but the Dess-Martin's oxydation [15] gave a mixture of lactone **16** and the expected dialdehyde **4** (65%, **16/4** = 70:30). However the compounds **16** and **4** were submitted to the crucial SmI_2 radical coupling reaction to give after purification the cyclic product **3** as well as recovered lactone **16** (**16/3** = 70:30, 95%).[16] X-ray analysis [17] of compound **3** shown that the two hydroxyl functions at C-6 and C-7 have the desired configurations.[18]



15 **16** **4**





ORTEP diagram

a) Dess-Martin (2eq), CH_2Cl_2, tBuOH (2eq) 20°C, 45min, then **15** 20°C, 2h, —> **16+4**, (65%, **16/4** = 70:30, NMR). b) **16+4**, SmI_2 (3-4eq), tBuOH (2eq), THF, -78°C—> 20°C, 2h,—> **16+3**, (95%, **16/3** = 70:30).

*In good agreement with previous intramolecular pinacolic couplings,[19] the SmI_2 mediated reaction of the dialdehyde **4** led to a cyclic cis-6,7 diol and quite remarquably to the 6β,7β diol required for forskolin synthesis. In spite of difficulties related to the preparation of the precursor dialdehyde **4**, this new approach*

appears to be promising to create the trans decalin AB system of forskolin **1**, *with subsequent introduction of the cis 6β,7β-diol, or more generally bicyclic compounds with vicinal diol .*

Efforts are now devoted to improve an adequate preparation of dialdehyde **4** *. The synthesis of Ziegler synthon* **2** *using a slight modified strategy is on current progress.*

References and Notes

1- Bhat, S.V.; Bajwa, B.S.; Dornauer,H.; deSouza, N.J.; Fehlhaber, H-W., *Tetrahedron Lett.*, **1977**, 1669-72.; Bhat, S.V.; Bajwa, B.S.; Dornauer, H.; deSouza, N.J., *J. Chem. Soc. Perkin Trans I*, **1982**, 767-71.

2- Seamon, K.B.; Daly, J.W., *Adv. Cyclic. Nucleotide Res.*, **1986**, *20*, 1-150.

3- Lichey, J.; Friedrich, T.; Priesnitz, M.; Biamino, G.; Usinger, P.; Huckauf, H., *Lancet*, **1984**, *2*, 167-170.

4- Erhardt, P.W., *J. Med. Chem.*, **1987**, *30*, 231-237.

5- Caprioli, J., *Drug. Dev. Res.* , **1985**, *6*, 193-215.

6- For a review see : Colombo, M.I.; Zinczuk, J.; Ruveda, E.A., *Tetrahedron*, **1992**, *48*, 963-1037, and references cited therein.

7- -a) Ziegler, F.E.; Jaynes, B.H.; Saindane, M.T., *Tetrahedron Lett.*, **1985**, *26*, 3307-3310.; *J. Amer. Chem. Soc.*, **1987**, *109*, 8115-16. -b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S., *J. Amer. Chem. Soc.*, **1988**, *110*, 3670-72. -c) Corey, E.J.; Da Silva Jardine, P; Rohloff, J.C., *J. Amer. Chem. Soc.*, **1988**, *110*, 3672-73. Enantioselective synthesis : Corey, E.J.; Bakshi, R.K.; Shibata, S., *J. Amer. Chem. Soc.*, **1987**, *109*, 5551-53.; Corey, E.J.; Da Silva Jardine, P.; Mohri, T., *Tetrahedron Lett.*, **1988**, *29*, 6409-12; Corey, E.J.; Da Silva Jardine, P., *Tetrahedron Lett.*, **1989**, *30*, 7297-7300.

8- See reference 6 and also : Fraser-Reid, B., *J. Org. Chem.*, **1992**, *57*, 1065-67; Blanchot-Courtois, V.; Fetizon, M.; Hanna, I., *Tetrahedron Lett.*, **1992**, *33*, 5061-64; Blanchot-Courtois, V.; Hanna, I.; Prange, T., *Tetrahedron Lett.*, **1992**, *33*, 5065-66.

9- Leclaire, M.; Levet, R.; Lallemand, J-Y., *Synth. Commun.*, **1993**, *23*, 1923-27.; Lallemand, J-Y.; Leclaire, M.; Levet, R.; Aranda, G., *Tetrahedron Asymmetry*, **1993**, *4*, 1775-78.

10- Namy, J.L.; Souppe, J.; Kagan, H.B., *Tetrahedron Lett.*, **1983**, *24*, 765-766.; Enholm, E.J.; Trivellas, A., *Tetrahedron Lett.*, **1989**, *30*, 1063-66.; Curran, D.P.; Fevig, T.L.; Jasperse, C.P.; Totleben, M.J., *Synlett*, **1992**, 943-961.

11- Nicolaou, K.C.; Li, W.S., *J. Chem. Soc. Chem. Commun.*, **1985**, 421.

12- Stork, G.; Malhotra, S.; Thompson, H.; Uchibayashi, M., *J. Amer. Chem. Soc.*, **1965**, *87*, 1148-49.; Stork, G.; Boeckmann Jr . R.K.; Taber, D.F.; Still, W.C.; Singh, J., *J. Amer. Chem. Soc.*, **1979**, *101*, 7107-7109.; Stork, G.; Singh, J., *J.Amer. Chem. Soc.*, **1979**, *101, 7109*.; Stork, G.; Mook, R., *J. Amer. Chem. Soc.*, **1987**, *109*, 2829-31.

13- All spectral data are consistent with proposed structures.

14- Chen, S-M.L.; Schaub, R.E.; Grudzinskas, C.V., *J. Org. Chem.*, **1978**, *43*, 3450-54.

15- Dess, D.B.; Martin, J.C., *J. Org. Chem.*, **1983**, *48*, 4155-6 ; Ireland, R.E.; Liu, L., *J. Org. Chem.*, **1993**, *58*, 2899.

16- In a typical experiment we first oxidize diol **15** with the Dess-Martin reagent as described; the crude residue was then submitted to the pinacolic coupling reaction and reduced with $LiAlH_4$ to give after purification the expected cyclic diol **3** and diol **15** in 15-20% and 40% yields respectively.

17- Compound **3** was cristallized in diethyl ether/petroleum ether as small colorless prisms. Space group P21/n with parameters a = 20.578(5); b = 8.009(3); c = 8.247(3) Å β = 99.9(1)° and Z = 4. The structure was solved by direct methods and refined to R = 8.2 (Rw=7.8%) for all data (1444 structure factors). The figure shows the ORTEP diagram with elipsoids drawn at the 50% probability level.

18- **3** : ^{1}H NMR ($CDCl_3$, 400MHz) : 0.98 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.18 (d, J = 6.3 Hz, 3H, CH_3), 1.3-1.4 (m, 3H, Ha-2 + CH_2-3), 1.5 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 1.97 (m, 1H, Hb-2), 2.16 (d, J = 2.6 Hz, 1H, H-5), 2.22 (d, J = 7.3 Hz, 1H, OH), 2.50 (dq, J = 9.6, 6.3 Hz, 1H, H-8), 3.01 (ddd, J = 9.6, 7.3, 3.1 Hz, 1H, H-7), 4.18 (dd, J = 9.0, 7.1 Hz, 1H, H-1), 4.24 (dd, J = 3.1, 2.6 Hz, 1H, H-6), 5.9 (d, J = 1.8 Hz, 1H, H-11). 13C NMR ($CDCl_3$, 50.31MHz) : 14.34 (CH_3), 24.78 (C-3), 26.08 (CH_3), 27.29 (CH_3), 30.26 (CH_3 + C-8), 30.87 (CH_3), 31.36 (C-4), 34.45 (C-2), 47.70 (C-10), 50.49(C-5), 71.38 (C-7), 80. 41 (C-6), 90.30 (C-1), 125.17 (C-9), 136. 54 (C-11).

19- Chiara, J.L.; Cabri, W.; Hanessian, S., *Tetrahedron Lett.*, **1991**, *32*, 1125-28, and references cited therein.

(*Received in France* 4 *July* 1994; *accepted* 27 *August* 1994)