Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5523-5526, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01187-2

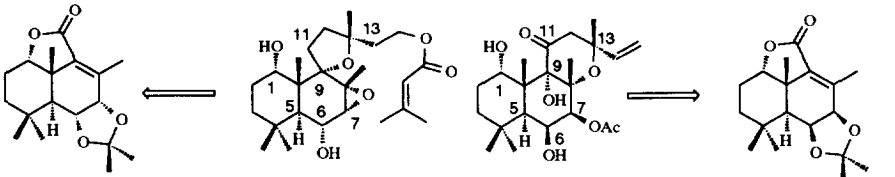
SmI_2 in a 6-Exo-Dig Radical Cyclisation in a Synthetic Approach to (±)-Erigerol

Claude Anies, Jean-Yves Lallemand, Ange Pancrazi *

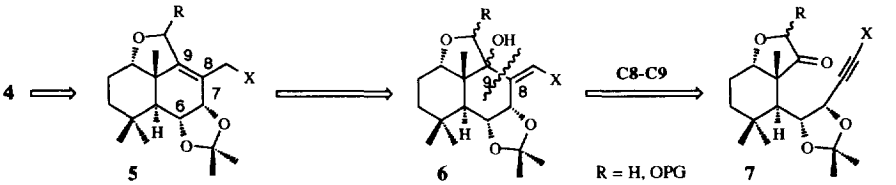
Laboratoire de Synthèse Organique, associé au CNRS, Ecole Polytechnique, DCSO, 91128, Palaiseau, France.

Abstract : In a synthetic approach of erigerol **2**, an intramolecular 6-exo-dig radical cyclisation was performed. Treatment of ynones **18** and **19** with SmI_2 gave in high yield the bicylic derivatives **20** and **21**. Copyright © 1996 Elsevier Science Ltd

In a synthetic approach to forskolin **1**,[1] our strategy was focused on the general formation of highly substituted *trans*-decalinic ring systems, and in preceding papers we described a formal synthesis of forskolin **1** [2] using cyclisation reactions promoted by samarium diiodide (SmI_2) or tributylstannyl hydride (Bu_3SnH) as key steps .[3] Erigerol **2** [4] presents a related terpenoid structure, and for these two compounds **1** [5] and **2**,[4] total syntheses were envisaged *via* the intermediate preparation of the analogous synthons **3** and **4** respectively.

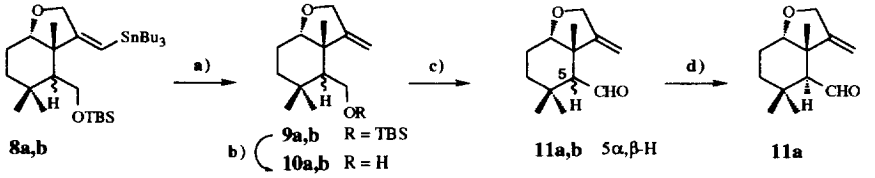


In order to develop new strategies for the synthesis of labdane diterpenes, we decided to pursue an approach of **4** *via* compounds **5** and **6** starting with ynone derivative **7**. As depicted below, the key step was the creation of the C8-C9 bond together with the introduction of a tertiary alcohol at C9.



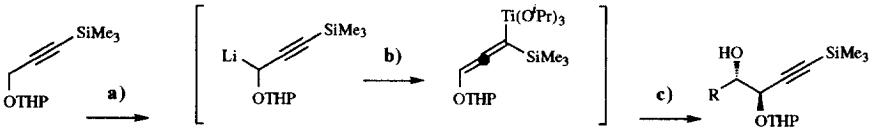
From a 1:1 mixture of epimeric vinylstannanes **8a,b** [6] a protodestannylation in acidic media gave the vinyl derivatives **9a,b**. After deprotection of the primary alcohol, compounds **10a,b** were oxidized with PCC [7] to furnish a 1:1 mixture of the 5α-H and 5β-H aldehydes **11a** and **11b**. At this stage a basic treatment of **11a,b** (K_2CO_3, MeOH, Δ) resulted in a complete isomerisation into the desired 5αH-isomer

11a. The 5α-H aldehyde **11a** was further converted into the acetylenic diol **16** (see below) *via* a reaction developed by Yamamoto.[8]



a) HCl 1N/THF 1:3, 20°C, 3 h. b) HF/CH_3CN 5:95, 20°C, 1 h, 75% yield from **8a,b**. c) PCC on celite, CH_2Cl_2, 20°C, 1.5 h, 85%. d) K_2CO_3, MeOH, Δ, 3 h, 90%.

Yamamoto's reagent **13** was prepared by metallation (*t*-BuLi, THF -78°C, 45 min.) of the propargylic ether **12**. After transmetallation using $Ti(O^iPr)_4$ (-78°C, 10 min.), the resulting allenyltitanium reagent **14** could then react with an aldehyde to furnish the *anti*-diol derivative **15** in good yield.[8]



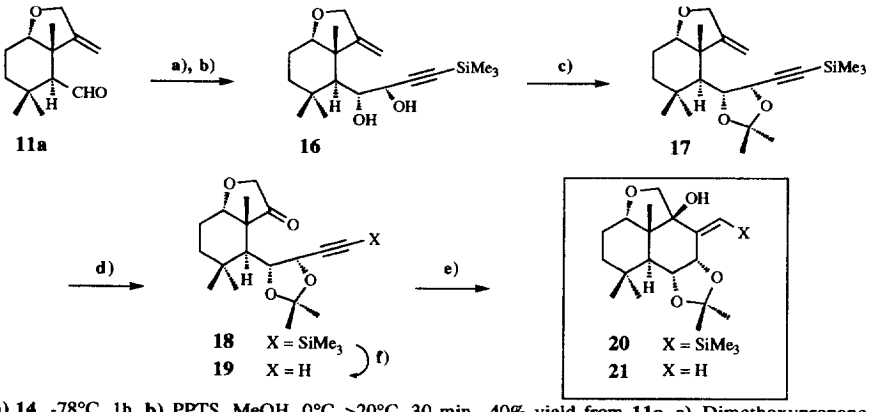
a) *t*BuLi, THF, -78°C, 45 min. b) $Ti(O^iPr)_4$, -78°C, 10 min. c) RCHO, -78°C, 40-75% for the three steps.

When the 5α-H aldehyde **11a** was treated with one equivalent of the titanium compound **14** no reaction occurred. However when two equivalents of this latter reagent were used, the expected reaction took place, and as expected, the *anti*-aldol **16** was obtained in 40% yield after acidic treatment of the crude tetrahydropyranyloxy intermediate.[9] Conversion of the diol **16** into the acetonide **17** was then achieved in 95% yield. A selective ozonolysis afforded the expected keto-acetylenic derivative **18** in 75% yield.[10] The compound **18** was treated with SmI_2 [11] and the cyclised derivative **20** was obtained in 90% yield. The 9β-OH structure of **20** was supported by ^1H NMR and ^{13}C NMR analysis together with NOE experiments.[12]

If a 5-exo-dig radical cyclisation is an efficient process,[13] the corresponding 6-exo-dig radical cyclisations promoted by SmI_2 have been described as moderate to low yielding reactions.[14] Our results showed that such a reaction was largely depending on the structure of the starting ynone, and could occur in good yield on **18**.

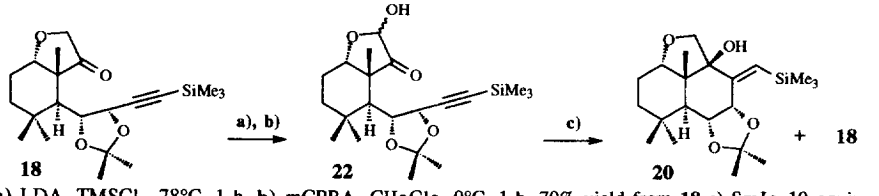
In the case of the desilylated derivative **19** the radical cyclisation again occurred in good yield. The 9β-OH stereochemistry was explained by an α approach of the yne-chain due to the particular structure of the bicyclic moiety.

In order to achieve our synthesis of the erigerol precursor **4**, we then focused on the cyclisation of the corresponding 11-hydroxy ynone **22**. Compound **18** was treated with LDA and TMSCl to furnish the corresponding silyl enol ether which was in turn oxidized with MCPBA to give **22** in 70% overall yield.[15] This keto-lactol **22** was then submitted to different acidic conditions (MeOH/HCl 2N, MeOH/amberlyst 15) but the desired OMe derivative could not be prepared in acceptable yield in such conditions.



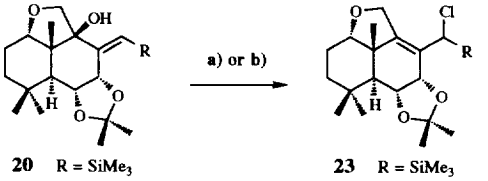
a) 14, -78°C, 1h. **b)** PPTS, MeOH, 0°C–>20°C, 30 min., 40% yield from **11a**. **c)** Dimethoxypropane, CSA, 20°C, 2 h, 95%. **d)** O_3, CH_2Cl_2, -78°C, Me_2S, -78°C–>20°C, 12 h, 75%. **e)** SmI_2 10 equiv, BuOH 5 equiv, THF, -78°C 1 h, 20°C, 2 h, 90%. **f)** K_2CO_3, MeOH, 20°C, 30 min., 95%.

Nevertheless we decided to perform our previous cyclisation reaction on the keto-lactol **22**. In the same preceding conditions, the reaction led to a 1:1 mixture of the two deoxygenated compounds **20** and **18**. Unfortunately, in this case, the deoxygenation encountered in α-hydroxyketones,[16] or in α-hydroxylactones,[17] is faster than the cyclisation reaction.



a) LDA, TMSCl, -78°C, 1 h. **b)** mCPBA, CH_2Cl_2, 0°C, 1 h, 70% yield from **18** **c)** SmI_2 10 equiv, BuOH 5 equiv, THF, -78°C, 1 h, then 20°C, 2 h, 75% **20/18** = 1:1.

In spite of this disappointing result, the penultimate step in our approach was successfully tested on the allylic alcohols **20** and **21**. These compounds were cleanly converted into the corresponding chloro-allyl compounds **23** and **24** with $SOCl_2$/ py.[18] The same reaction occurred on **20** and **21** with MsCl/ Py.



a) $SOCl_2$, Py, 20°C, 1 h 85%. **b)** MsCl, NEt_3, CH_2Cl_2, 20°C, 1 h, 80%.

*This study of a radical approach to erigerol **2** using SmI_2 gives us an original and efficient method for the construction of highly substituted trans-decalinic skeletons encountered in many natural diterpenes. Our efforts are now focused on an allylic oxidation of derivative **23** for the synthesis of the unsaturated lactone synthon **4**.*

References and Notes :

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

(2) Anies, C.; Pancrazi, A.; Lallemand, J.Y. *Tetrahedron Lett.* **1995**, *36*, 2075-78.

(3) Anies, C.; Billot, L.; Lallemand, J.Y.; Pancrazi, A. *Tetrahedron Lett.* **1995**, *36*, 7247-50.

(4) Total synthesis of erigerol: Kienzle, F.; Stadlwieser, J.; Rank, W.; Mergelsberg, I. *Tetrahedron Lett.* **1988**, *29*, 6479-82. Kienzle, F.; Stadlwieser, J.; Rank, W.; Schönholzer, P. *Helv. Chim. Acta* **1990**, *73*, 1108-38. Synthetic approaches: a) Colombo, M. I.; Zinczuk, J.; Bacigaluppo, J. A.; Somoza, C.; Ruveda, E. A. *J. Org. Chem.* **1990**, *55*, 5631-39 and references cited therein. b) Preite, M. D. ; Ruveda, E. A. *Synth. Commun.* **1994**, *24*, 2809-25.

(5) For total synthesis of forskolin see: -a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307-10. Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115-16. -b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S., *J. Am. Chem. Soc.* **1988**, *110*, 3670-72. -c) Corey, E. J.; Da Silva Jardine, P; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672-73. 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*, 7297-300. -d) Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1015-18. *ibid* **1996**, *37*, 1019-22. Calvo, D.; Port, M.; Delpech, B.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1023-24. For a review see: Colombo, M. I.; Zinczuk, J.; Ruveda, E. A. *Tetrahedron*, **1992**, *48*, 963-1037, and references cited therein. For a recent formal synthesis of forskolin see ref 2.

(6) Anies, C.; Pancrazi, A.; Lallemand, J.-Y.; Prange, T. *Tetrahedron Lett.* **1994**, *35*, 7771-72.

(7) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-50.

(8) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225-27. Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568-70. Ishiguro, M.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 1029-30. See also Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, 5041-43. Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 1815-16. Leroux, Y.; Roman, C. *Tetrahedron Lett.* **1973**, 2585-86. For an asymetric aldol reaction using a propargylic titanium reagent and (-)-sparteine see Dreller, S.; Dyrbusch, M.; Hoppe, D. *Synlett* **1991**, 397-400. For reaction with allenic zincate see Harada, T.; Osada, A.; Oku, A. *Tetrahedron Lett.* **1995**, *36*, 723-24.

(9) Anies, C.; Lallemaand, J.-Y.; Pancrazi, A. *Tetrahedron Lett., accompanying note.*

(10) **18:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.2 [s, 9H, $3CH_3$, $Si(CH_3)_3$], 1.10 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.30 (m, 1H), 0.80-1.9 (m, 3H), 2.24 (d, *J* = 8.9 Hz, 1H, H-5), 3.71 (t, *J* = 2.5 Hz, 1H, H-1), 3.83 (d, *J* = 17.0 Hz, 1H, H-11a), 4.12 (dd, *J* = 8.9, 5.0 Hz, 1H, H-6), 4.38 (d, *J* = 17.0 Hz, 1H, H-11b), 4.71 (d, *J* = 5.0 Hz, 1H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -0.2 [$3CH_3$, $Si(CH_3)_3$], 14.9 (CH_3), 22.1 (C-3), 22.4 (CH_3), 25.9 (CH_3), 27.5 (CH_3), 34.2 (CH_3), 34.5 (C-4), 36.4 (C-2), 42.8 (C-5), 49.0 (C-10), 70.8 (C-11), 70.9 and 77.8 (C-6 + C-7), 84.3 (C-1), 93.9 (C-8), 103.7 (CCSiMe3), 109.5 (O-C(CH_3)$_2$-O), 218.2 (C=O, C-9).

(11) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc* **1980**, *102*, 2693-98. Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765-66. 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**, 943-61.

(12) **20:** To a solution of samarium iodide (15 mL, 1.5 mmol, 10 equiv) cooled to -78°C was added a solution of the ketone **18** (54 mg, 0.14 mmol) and *t*-butyl alcohol (71 mL, 0.74 mmol, 5.0 equiv) in dry THF (10 mL), which had been precooled to - 78°C. After stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of saturated NH_4Cl solution. This was then extracted with ethyl acetate twice and the combined extracts were washed successively with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and concentration *in vacuo*, the resulting oil was chromatographed on silica gel eluting with petroleum ether/ethyl acetate to give compound **20** (48 mg, 90% yield).
^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.18 [s, 9H, $3CH_3$, $Si(CH_3)_3$], 0.95 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.22-1.56 (m, 3H, H-2a and H_2-3), 1.38 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.53 (d, *J* = 11.4 Hz, 1H, H-5), 1.6 (m, 1H, OH), 1.78-1.84 (m, 1H, H-2b), 3.77 (d, *J* = 9.5 Hz, 1H, H-11a), 4.0 (t, *J* = 4.4 Hz, 1H, H-1), 4.27 (d, *J* = 9.5 Hz, 1H, H-11b), 4.34 (dd, *J* = 11.4, 6.1 Hz, 1H, H-6), 4.81 (d, *J* = 6.1 Hz, 1H, H-7), 6.39 (s, 1H, H-8'). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 0.4 [$3CH_3$, $Si(CH_3)_3$], 12.5 (CH_3), 23.2 (CH_3), 23.4 (C-3), 25.9 (CH_3), 28.4 (CH_3), 32.9 (C-4), 34.3 (CH_3), 35.8 (C-2), 44.7 (C-5), 48.6 (C-10), 75.8 and 75.9 (C-6 + C-7) , 78.6 (C-11), 82.9 (C-1), 85.3 (C-9), 108.3 (O-C(CH_3)$_2$-O), 136.8 [C=CH($SiMe_3$)], 151.9 (C-8).

(13) Molander, G. A.; McKie, J. A. *J. Org. Chem* **1995**, *60*, 872-82. For a review see also, Molander, G. A. *Chem Rev* **1992**, *92*, 29-68.

(14) Shim, S. C.; Hwang, J. T.; Kang, H.-Y.; Chang, M. H. *Tetrahedron Lett.* **1990**, *31*, 4765-68.

(15) **22:** major isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.2 [s, 9H, $3CH_3$, $Si(CH_3)_3$], 1.12 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.3-1.9 (m, 4H, $H_2$2 + $H_2$3), 1.25 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.18 (d, *J* = 9.5 Hz, 1H, H-5), 4.08 (dd, *J* = 9.5, 5.0 Hz, 1H, H-6), 4.1 (t, *J* = 3.5 Hz, 1H, H-1), 4.65 (d, *J* = 5.0 Hz, 1H, H-7), 5.55 (s, 1H, H-11). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ - 0.3 [$3CH_3$, $Si(CH_3)_3$], 15.2 (CH_3), 21.8 (C-3), 22.7 (CH_3), 26.0 (CH_3), 27.5 (CH_3), 33.9 (CH_3), 34.5 (C-4), 36.4 (C-2), 43.4 (C-5), 49.1 (C-10), 70.7 and 78.4 (C-6 + C-7), 81.8 (C-1), 93.4 (CC-H), 103.6 (C-8), 108.6 (O-C(CH_3)$_2$-O), 115.5 (C-11), 214.7 (C=O, C-9).

(16) Enholm, E. J.; Jiang, S.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061-69.

(17) Hanessian, S.; Girard, C.; Chiara, J. L. *Tetrahedron Lett.* **1992**, *33*, 573-76.

(18) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901-30.

(*Received in France* 6 *May* 1996; *accepted* 13 *June* 1996)