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# A RADICAL CYCLISATION ROUTE TO (±)-ANDIROLACTONE, A SPIRO-γ-BUTYROLACTONE

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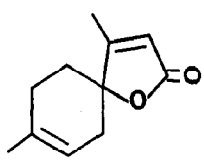
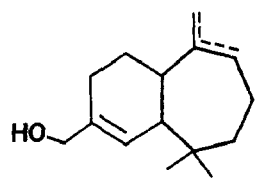
Abstract: Synthesis of Andirolactone (1), starting from 4-methyl cyclohex-3-en-1-one (5), via the radical cyclisation of the bromoacetal (7), is described.

Andirolactone (1), a desisobutenyl sesquiterpene containing a spiro-γ-butyrolactone moiety, was isolated recently from the medicinal plant, Cedrus libanotica along with three other terpenoids, two hydroxy himachalenes (torosols 2 & 3) and trans-atlanton-6-ol 4.[1] Currently radical cyclisation reaction is widely accepted as a powerful tool in organic synthesis and its utility to various butyrolactones is well documented.[2,3] In this communication, we now describe the synthesis[4] of andirolactone (1) starting from the readily available[5] 4-methyl cyclohex-3-en-1-one (5) using radical cyclisation reaction as the key step.




1

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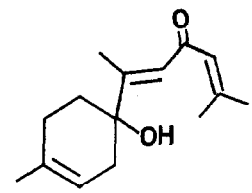
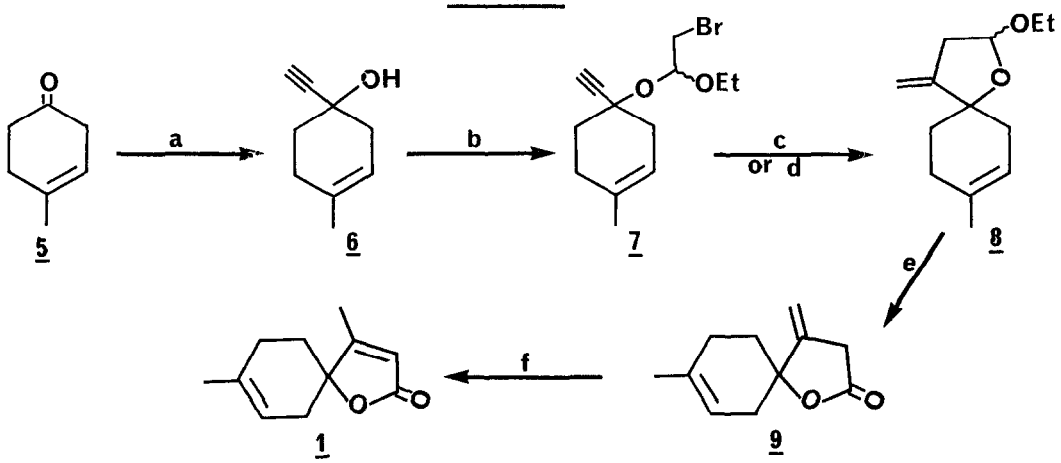



4

The synthetic sequence is depicted in the scheme; the radical cyclisation of the bromoacetal 7, obtained from the acetylenic alcohol 6, generates the hemiacetal 8, which on oxidation and isomerisation leads to spirolactone 1.[3b] Thus, addition of ethynyl magnesiumbromide to the enone 5, obtained from p-cresol,[5] resulted the acetylenic alcohol 6 in 50% yield.[6] The alcohol 6 was converted to the key radical precursor, bromoacetal 7, by treatment with a freshly prepared dibromoethyl ethyl ether (from ethyl vinyl ether and bromine) in methylene chloride in the presence of N,N-dimethyl aniline. The crucial radical cyclisation of the bromoacetal 7 to the hemiacetal 8 was carried out by refluxing a 0.02M benzene solution of 7 with 1.1 equiv. of tributyl tin-hydride (TBTH) in the presence of a catalytic amount of azobisisobutyro nitrile (AIBN). Alternatively, the cyclisation can also be carried out by using in situ generated catalytic TBTH (0.15 equiv. of n-$Bu_3SnCl$ or $Ph_3SnCl$ and 1.2 equiv. of $NaCNBH_3$)[3d] in t-butanol in the presence of catalytic AIBN with almost equal efficiency. The cyclised hemiacetal 8 was directly oxidised to the β-methylene lactone 9 with Jones reagent. Lactone 9 was found to be

**SCHEME**




a. ≡-MgBr, THF, RT, 1h, 50%; b. $BrCH_2CHBrOEt$, $PhNMe_2$, $CH_2Cl_2$, RT, 18h, 72%; c. TBTH (1.1eq.), $C_6H_6$, AIBN, 80°C, 1.5h, 74%; d. n-$Bu_3SnCl$ or $Ph_3SnCl$ (0.15 eq.), $NaCNBH_3$ (1.5eq.), t-BuOH, AIBN, 80°C, 1.5h, 70%; e. 1.2M Jones reagent, Acetone, RT, 1h; f. Silica gel, 81% from 8.

too labile and it was isomerised to the andirolactone (1) on attempted purification over silica gel column. The synthetic andirolactone exhibited spectral data identical to that of natural material.

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**References and notes:**

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2. M. Ramaiah, Tetrahedron, 43 3541 (1987); D.P. Curran, Synthesis, 417, (1988).
3. a. G. Stork, R. Mook,Jr., S.A. Biller and S.D. Rychnovsky, J. Am. Chem. Soc., 105, 3741 (1983); b. O. Moriya, M. Okawara and Y. Ueno, Chem. Lett., 1437 (1984); c. Y. Ueno, O. Moriya, K. Chino, M. Watanabe and M Okawara, J. Chem. Soc., Perkin Trans. I, 1351 (1986) and references cited there in; d. A. Srikrishna, J. Chem. Soc., Chem. Commun., 587 (1987); e. J.P. Dulcere, M.N. Mihoubi and J. Rodriguez, J. Chem. Soc., Chem. Commun., 237 (1988).
4. To our knowledge this is the first synthesis of the andirolactone.
5. E.J. Corey and D.S. Watt, J. Am. Chem. Soc., 95, 2303 (1973).
6. Selected spectral data **for 6**: IR (neat), 3410, 3300, 2120 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$): $\delta$ 5.27 (1H,brs), 2.49 & 2.31 (2H,AB q,J=17Hz), 2.43 (1H, s), 2.14 (2H,m), 1.91 (2H,m), 1.69 (3H,s); **for 7** (1:1 mixture of diastereomers): IR (neat), 3300, 2120 $cm^{-1}$, $^1H$ NMR (60 MHz, $CDCl_3$): $\delta$ 5.13 (2H,m), 3.2-3.8 (2H,m), 3.25 & 3.27 (2H,2xd,J=6Hz), 2.4 (1H,s), 1.83-2.53 (6H,m), 1.67 (3H,brs), 1.24 (3H,t,J=7Hz); **for 8** (1:1 mixture of diastereomers): IR (neat), 1660, 1000, 895 $cm^{-1}$, $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 5.37 (1H,m), 4.8-5.2 (3H,m), 3.3-3.95 (2H,m), 2.4-3.1 (2H,m), 1.0-2.4 (6H,m), 1.72 (3H,s)

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