Pergamon

Tetrahedron Letters 43 (2002) 8277–8279

TETRAHEDRON LETTERS

Synthesis of agarofuran antifeedants. Part 3: Synthesis of polyhydroxylated *pyrano*-agarofurans†

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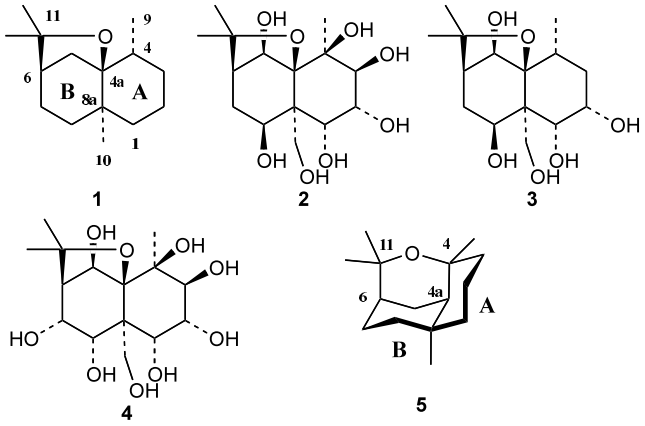
Received 27 August 2002; accepted 16 September 2002

Abstract—The synthesis of *pyrano*-agarofurans is described using as key step the stereoselective epoxidation of a 6α-hydroxy-1,2,3,4,6,7,8,8a-octahydronaphtalene derivative **8** controlled by the configuration of the allylic alcohol at C-6.

Beside numerous diterpenic natural products isolated from higher plants for their antifeedant activity on insects, the esters of agarofuran (**1**) sesquiterpenes polyols represent a quite amazing family of compounds due to their structural diversity, their numerous biological activities and their abundance in the *Celastraceae* family.[1] The most commonly encountered derivatives of this family are esters of maytol **2**, 3,4-dideoxy maytol **3** and euonyminol **4**.



1 **2** **3** **4** **5**

However, the key structural feature of these compounds lies in the tetrahydrofuran ring formed through the ether linkage between carbon atoms C-11 and C-4a in a *trans* configuration of the decalinic system A/B.[2]

Noteworthy, one should also consider an interesting, but very poorly investigated natural product, evuncifer ether **5**, a major constituent of the defense secretion of the termite *Amitermes evuncifer*.[3] Indeed, this eudesmane sesquiterpene is very similar to agarofurans apart from the size of the heterocycle, which is in this case a tetrahydropyran involving an ether linkage between carbon atoms C-11 and C-4 in a *cis* configuration of bicycle A/B.

The presence in most of the more functionalised agarofuran esters of the *Celastraceae* of an hydroxy group at C-4, prompted us to investigate, beside the synthesis of the natural *furano*-agarofurans, a possible equilibrium between these natural compounds and their unreported *pyrano*-agarofurans analogues related to evuncifer ether, through isomerisation of the decalinic ring junction.

In this paper, we report the synthesis of a *pyrano*-agarofuran tetraol starting from hexahydronaphtalenone **6**, synthesis of which has been reported in our first report of this series.[4]

The first step of the synthesis requires the allylic oxidation of the $\Delta^{4a,5}$ double bond which is achieved through treatment with dimethyldioxirane (DDO) in acetone‡ and afforded enone **7** in 76% yield. Then, according to our previously reported procedure for heterocycle construction,[5] reduction of both keto groups and epoxidation of the double bond yielded stereoselectively

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† For Part 2, see: Ref. 5a.

‡ The quite peculiar scope of this reaction will be discussed elsewhere.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02027-0

epoxide **9**. In this case indeed, the stereochemistry of the epoxidation step (**8**→**9**), performed using *m*-CPBA as peracide is preferentially controlled by the configuration of the secondary equatorial hydroxy group at C-6 rather than the tertiary alcohol at C-4.[6] Thereafter esterification of the hydroxy group at C-6 as its triflate and treatment with tetraethylammoniumcyanide afforded through a clean S_N2 process cyanoepoxide **11** (Scheme 1).

At this point of our work, we were quite confident of the stereochemical issue of the epoxidation step, due to our previous experience on model compounds,[5a] but NMR data of cyanoepoxide **11**[7] were somewhat surprising and forced us to assume, after molecular modelisation studies and NOE experiments, a boat-like conformation of cycle B of the decalinic system, which thus allowed both hydroxy groups at C-1 and C-4 and *t*-butyldimethylsilyloxy group at C-8 to be in equatorial positions, while methyl at C-4 and cyano group at C-6 were axial (Fig. 1, left). Thereafter, the reduction of the cyano group afforded the expected vinylic aldehyde **12** through concomitant fragmentation of the epoxide ring due to the basicity of the aluminohydride. In fact, spontaneous ring opening of epoxide **11** was also observed on standing, affording the α,β-unsaturated nitrile **13**, as a well crystallised compound suitable for X-ray analysis[8] (Fig. 1, right—only H of interest are shown). This study allowed the unambiguous attribution of the configuration of the stereogenic centres and of the *cis* configuration of the decalinic system.

Catalytic hydrogenation of the $\Delta^{5,6}$ double bond occurred thereafter from the α-face of the molecule and gave a mixture of ketals **14a**,**b** and aldehyde **15** (Scheme 2). Direct oxidation of this mixture (Jones' reagent) afforded the desired δ-lactone **16** in 90% yield. Introduction of the two methyl groups was then effected in a two step procedure since even treatment with a large excess of methyl lithium only afforded ketal **17**. However, **17** was further subjected to the action of trimethyl aluminium in the presence of boron trifluoride etherate[9] to achieve the formation of dimethyl tetrahydropyran **18** in 60% yield. Reduction of the ester group and deprotection of the hydroxy group at C-8 then cleanly afforded the desired *pyrano*-agarofuran **20**.[7]

In order to study the possibility of an equilibrium between *furano*- and *pyrano*-agarofurans, we then subjected compounds **17** and **20** to a drastic acidic treatment in aqueous conditions. *pyrano*-Agarofuran **20** remained unchanged while ketal **17** afforded in 50% yield isomeric ketal **21** corresponding to a *furano*-agarofuran precursor (Scheme 3).

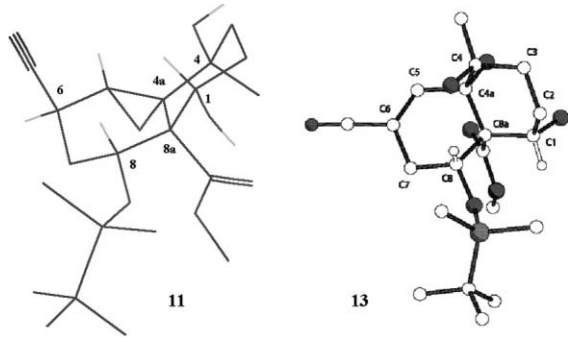
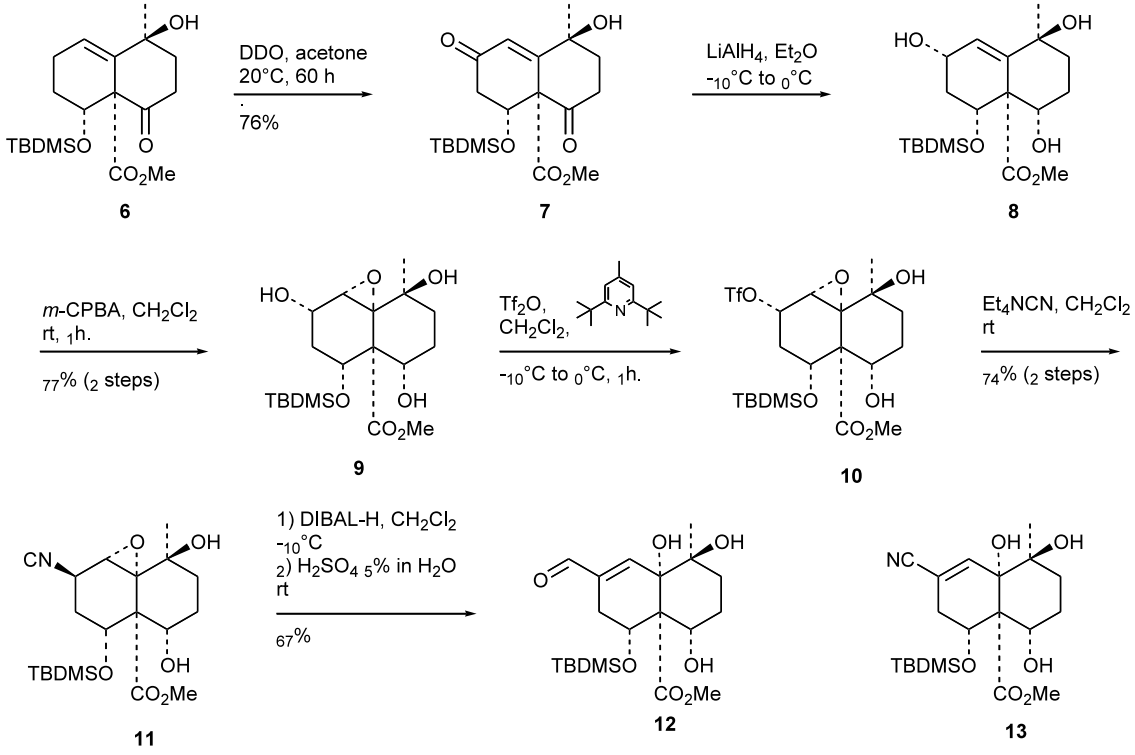
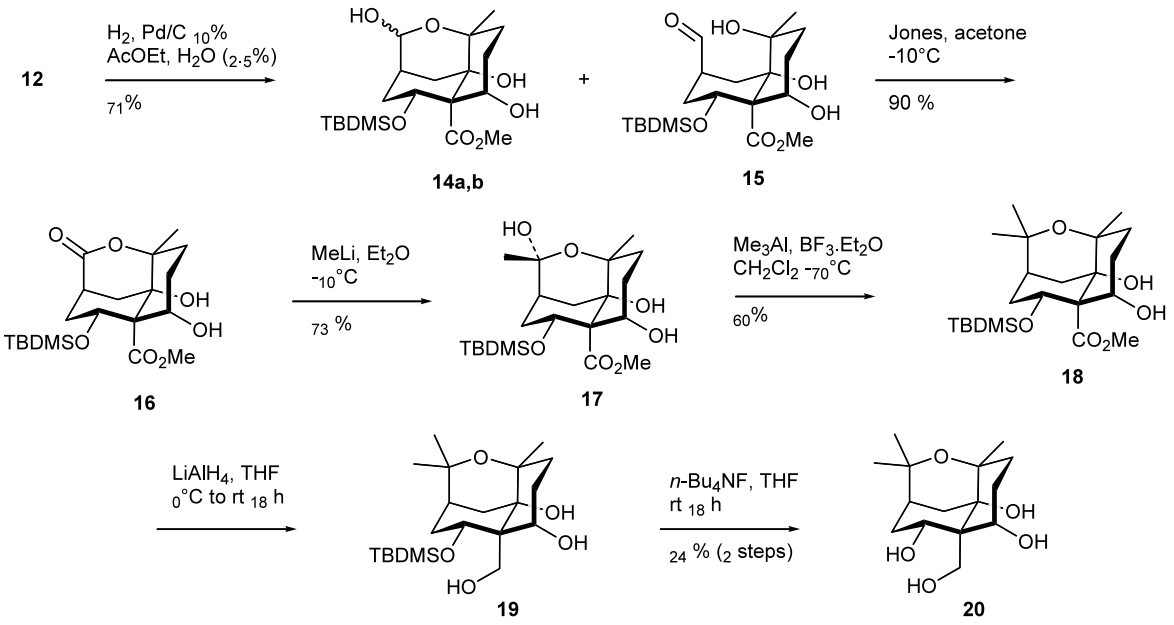


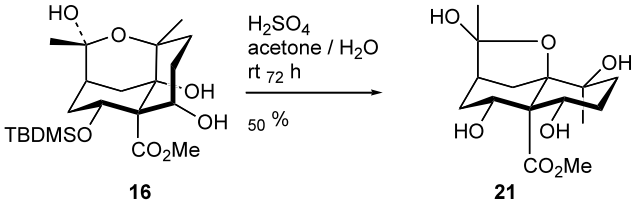
Figure 1.



Scheme 1.



Scheme 2.



Scheme 3.

These results show that the *cis*-decalinic system can be isomerised, through formation of a carbocation at C-4a into the thermodynamically more stabilised *trans*-decalin. However, this process, starting from *pyrano*-agarofuran **20**, in order to yield its *furano*-agarofuran analogue would have required the preliminary tetrahydropyran ring opening through formation and quenching by water of a carbocation either at C-4 or C-11. The intramolecular process, leading back to **20**, is however much faster and therefore does not allow the desired ring junction isomerisation to occur.

Synthesis of *furano*-agarofurans using the same precursor **6** and biological investigations on the *pyrano*-agarofuran esters will be reported in due time.

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7. Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30 (dd, $J=11$, 5 Hz), 4.01 (d, $J=12$ Hz, OH), 3.79 (d, $J=4$ Hz), 3.72 (s, 3 H), 3.57 (td, $J=12$, 4.5 Hz), 3.37 (dd, $J=7$, 4 Hz), 2.18 (ddd, $J=13$, 11, 5 Hz), 2.05–1.50 (m, 5 H), 1.17 (s, 3 H), 0.81 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2 (s), 118.4 (s), 78.4 (d), 71.7 (d), 70.5 (s), 65.1 (s), 55.3 (s), 52.9 (d), 51.7 (q), 34.3 (t), 29.3 (t), 28.3 (t), 25.7 (3 C, q), 24.1 (q), 17.9 (s), –4.7 (q), –4.8 (q) ppm.
   Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (dd, $J=8$, 6 Hz), 4.58 (bs), 4.38 (bd, $J=12$ Hz), 4.30 (d, $J=12$ Hz), 4.14 (s, OH), 3.07 (s, OH), 3.04 (s, OH), 2.20–2.12 (m, 2 H), 2.00 (dt, $J=13.5$, 4.5 Hz), 1.82–1.52 (m, 5 H), 1.40 (dd, $J=13.5$, 3 Hz), 1.34 (s, 6 H), 1.21 (s, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.1 (s), 74.2 (s), 72.5 (s), 70.5 (d), 68.9 (d), 61.3 (t), 48.4 (s), 39.4 (d), 33.9 (t), 30.9 (t), 30.0 (t), 29.0 (t), 28.6 (q), 26.0 (q), 23.0 (q) ppm.
8. Monoclinic, space group $P2_1/c$; parameters: $a=12.506(3)$, $b=14.029(3)$, $c=12.717(3)$ Å, $\beta=97.23(5)°$, $Z=4$ ($T=100$ K). Anisotropically refined, $R=0.047$ (for 1985 observed F); $R_w=0.122$ (for all 1997 F^2). Coordinates have been deposited with the Cambridge Crystallographic Centre, ref. no. CCDC 189948.
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