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SYNTHESIS OF (+)-PACHYDICTYOL-A[1]

Andrew E. Greene
Laboratoire de Chimie Organique, C.E.R.M.O.
Université Scientifique et Médicale, 38041 Grenoble, France

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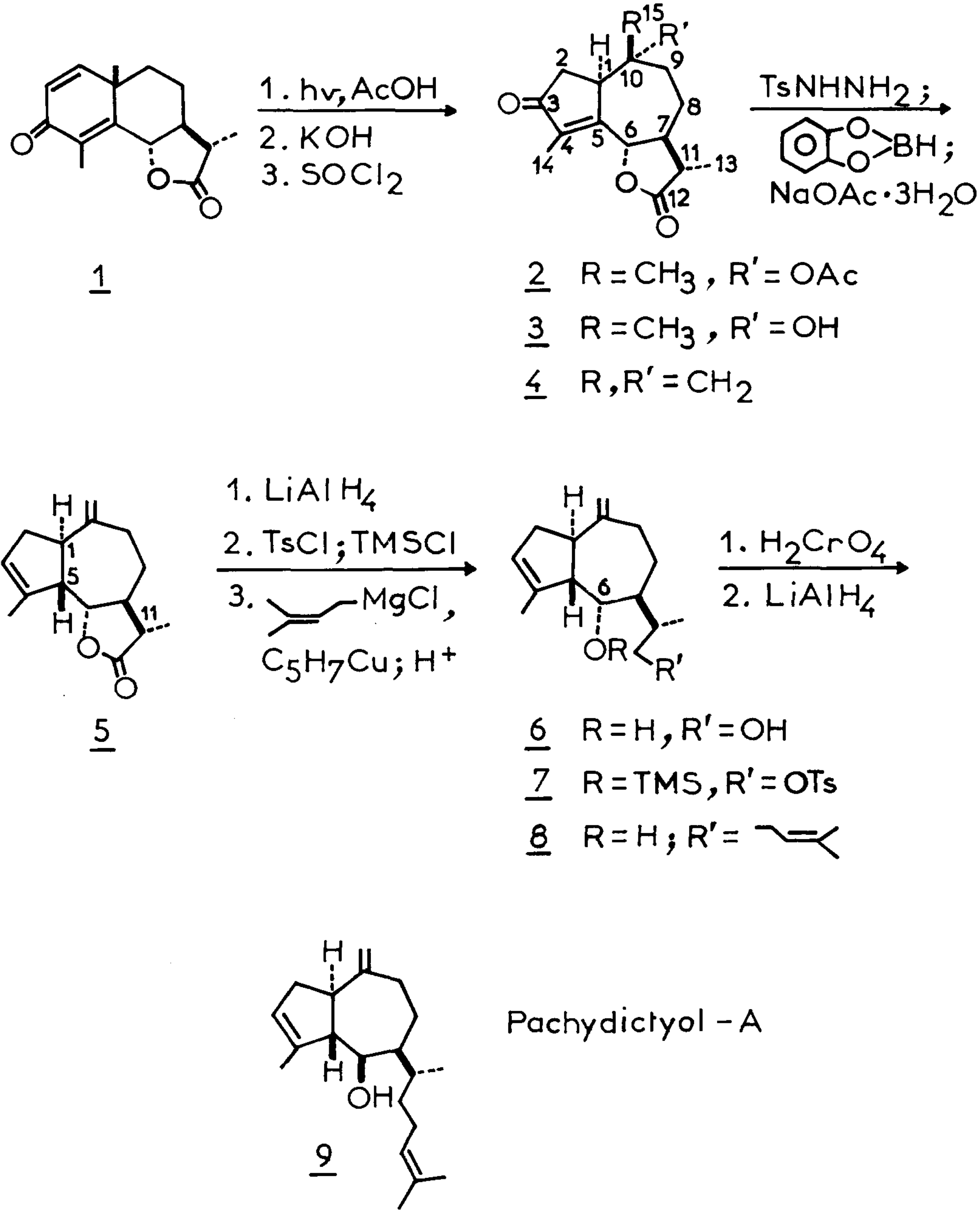
The diterpene alcohol pachydictyol-A (9), isolated from the brown marine alga Pachydictyon coriaceum (Dictyotaceae), was structurally and stereochemically elucidated by X-ray crystallography and was shown to possess the hydroazulene skeleton, previously unknown among the diterpenes[2]. Interestingly, pachydictyol-A exhibits mild antibiotic activity vs. Staphyloccus aureus. We wish to report a short, highly stereoselective synthesis of the natural material from (-)-α-santonin using as the key step a reductive transposition that introduces the correct trans ring fusion.

α-Santonin (1) is easily converted[3,4,5] by photochemical rearrangement, hydrolysis, and dehydration to the known[4] crystalline dienone-lactone 4. This intermediate not only possesses the general framework of pachydictyol-A but in addition the correct absolute stereochemistry at 3 of the 4 asymmetric centers and the C-10 exocyclic methylene unit already in place. This last feature was considered to be important due to the otherwise general difficulty in cleanly transforming such tertiary C-10 alcohols to the corresponding exocyclic methylenes[6].

Treatment[7] of the conjugated ketone 4 sequentially with p-toluenesulfonylhydrazine, catecholborane and sodium acetate produced the Δ^3-olefin 5, homogeneous by VPC and TLC[8], in 55% yield after purification on silica gel [$[\alpha]_D^{30} = +1.8°$ (c, 1.7, $CHCl_3$) ; I.R. ν(film) 3080, 3040, 1775, 1640, 895 cm^{-1} ; N.M.R. δ(CCl_4) 5.33 (br. s., 1-H), 4.82 (br. s., 2-H), 4.27 (t, J=9 Hz, 1-H), 1.88 (s, 3-H), 1.15 ppm (d, J=6 Hz, 3-H) ; m/e 232 (M^+)].

The trans ring fusion assignment[9] in 5 was arrived at by analogy with the results obtained using enone 2. Treatment of 2 under the aforementioned conditions smoothly afforded a crystalline compound 10 (5, where $<^{CH_3}_{OAc}$ replaces the exocyclic methylene) [mp 117-118° ; $[\alpha]_D^{24} = -35°$ (c, 1.7, $CHCl_3$)] that was clearly different from the known cis-fused product (1-α, 5-α H's) [mp 66-67° ; $[\alpha]_D^{24} = +8°$ (c, 1.7, $CHCl_3$)][5] although the IR and NMR spectra were quite similar to those reported for the latter. Oxidation (SeO_2 ; Jones) of 10 gave back 2, albeit in low yield as was the case with the cis-fused product[5], strongly suggesting that the only difference between the two is the stereochemistry at C-5, i.e. compound 10 must have 5-β hydrogen and thus be trans-fused[10].


1
1. hν, AcOH
2. KOH
3. SOCl$_2$
2 R = CH$_3$, R' = OAc
3 R = CH$_3$, R' = OH
4 R, R' = CH$_2$
TsNHNH$_2$;
BH;
NaOAc·3H$_2$O
5
1. LiAlH$_4$
2. TsCl; TMSCl
3. MgCl, C$_5$H$_7$Cu; H$^+$
6 R = H, R' = OH
7 R = TMS, R' = OTs
8 R = H; R' =
1. H$_2$CrO$_4$
2. LiAlH$_4$
9
Pachydictyol - A

After considerable study, it was found that "prenylation" of lactone 5 could be effectively carried out as follows. Lithium aluminum hydride reduction of 5 gave diol 6, as a gum, which was treated at -30° in pyridine first with excess *p*-toluenesulfonyl chloride (TsCl) and then with excess chlorotrimethylsilane (TMSCl). The resulting primary tosylate 7, essentially free of tetrahydrofuran side products, was immediately subjected to a coupling reaction with 3-methyl-2-butenylmagnesium chloride and 1-pentynylcopper in ether[11], which was then followed by brief exposure to acid to afford 6-*epi*-pachydictyol-A (8) in 30-40% overall yield from lactone 5 [$[\alpha]_D^{30}$ = +67° (c, 1.7, cyclohexane) ; I.R. ν(film) 3080, 3040, 1635, 885 cm^{-1} ; N.M.R. δ(CCl$_4$) 5.36 (br. s., 1-H), 5.00 (t, J=6 Hz, 1-H), 4.58 (br. s., 2-H), 3.86 (m, 1-H), *ca*. 1.7 (2s, 9-H), 0.83 ppm (d, J=7 Hz, 3-H) ; m/e 288 (M$^+$)].

As we had observed using pachydictyol-A, the ketone derived from alcohol 8 (or 9) by oxidation with aqueous chromic acid—ether[12] underwent a remarkably stereoselective reduction (*ca*. 90% 9 and 10% 8) with lithium aluminum hydride in ether at -77° to afford after purification on silica gel (+)-pachydictyol-A (9). This material [$[\alpha]_D^{30}$ = +98° (c, 0.8, cyclohexane), lit.[2] $[\alpha]_D^{30}$ = +106° (cyclohexane) ; α-naphthylurethane derivative mp 114-115°, lit.[2] α-naphthylurethane derivative mp 114-115°] was chromatographically and spectroscopically indistinguishable from an authentic sample of the natural product.

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8. Exposure of **5** to potassium *t*-butoxide in *t*-butanol afforded a mixture of **5** and its C-11 methyl epimer, which were well separated on TLC, thus giving a further indication of the homogeneity of this compound.
9. Proton NMR determination of the C-5 stereochemistry is rather unreliable. See, for example, reference 5.
10. The stereoselective formation of **5** from **4** and **10** from **2** at first appears surprising in view of the fact that hydrogenation[5] and certain 1,4 -reductions of **2** afford nearly exclusively the *cis*-fused system. These results, however, are consistent with the proposed reaction mechanism[7].
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