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Asymmetric Syntheses of Isostegane Derivatives using Trivalent Iodine Reagents

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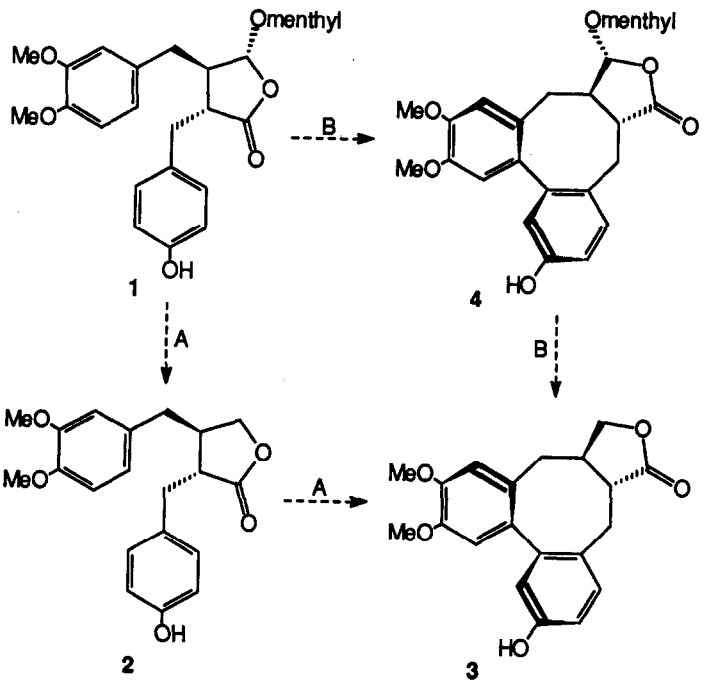
Abstract: Two asymmetric syntheses of the isostegane derivative (+)-**7** are reported, both involving oxidation of a homochiral 2,3-dibenzylbutyrolactone with phenyliodonium bis(trifluoroacetate). Of particular interest is the fact that the oxidative cyclisation leading to the biaryl link can be carried out directly on a precursor containing a hemiacetal functional group.

We have previously shown that phenyliodonium diacetate (PIDA) and phenyliodonium bis(trifluoroacetate) (PIFA) can be used to bring about two electron oxidation of phenols leading to quinone-monoketals and cyclohexa-2,5-dienones.[1,2] We have also shown that in the absence of an external nucleophile these reagents can be used to bring about intramolecular oxidative coupling leading, in the case of 2,3-dibenzylbutyrolactones, to spirodienones and dibenzocyclooctadiene lignans.[3] We have now adapted these reactions to provide an asymmetric synthesis of such compounds by starting with the homochiral dibenzylbutyrolactone (-)-**1**.

We envisaged two possible routes from **1** to compounds of the dibenzocyclooctadiene series (Scheme 1). The first (route A) would involve removing the menthyloxy group from **1** to give the homochiral dibenzylbutyrolactone (**2**). We have previously shown that treatment of *racemic* **2** with PIFA gives the isostegane derivative **3**.[3] The second route (route B) would involve treating **1** directly with PIFA which would be expected to give the menthyloxy substituted dibenzocyclooctadiene **4**. Removal of the menthyloxy substituent from **4** would then give the parent dibenzocyclooctadiene **3** (or a stereoisomer).

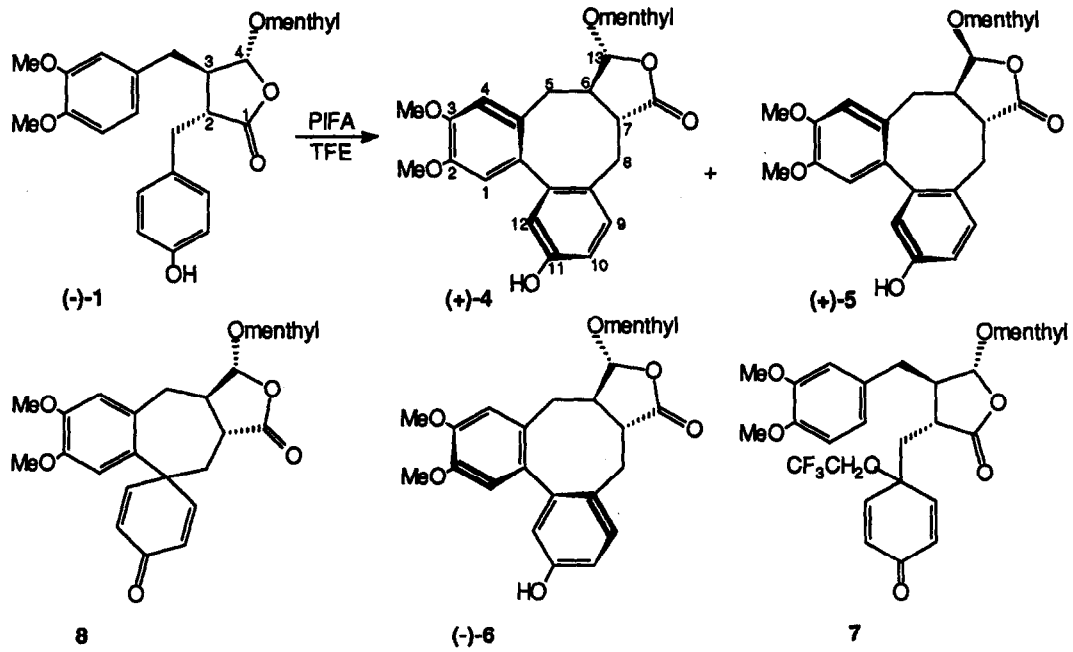
The dibenzylbutyrolactone (-)-**1**, $[\alpha]_D$ -145.8 (c = 0.402, $CHCl_3$) was prepared using the tandem conjugate addition methodology developed in these laboratories[4] and will be described in a full paper. Treatment of (-)-**1** with PIFA in trifluoroethanol (TFE) for 24 hours gave a mixture of products which were purified by chromatography to give the isostegane derivatives (+)-**4**, $[\alpha]_D$ + 186.9 (c = 0.312, $CHCl_3$) and (+)-**5**, $[\alpha]_D$ + 84.3 (c = 0.325, $CHCl_3$) in 44% combined yield along with minor amounts (5% and 2% respectively) of the stegane isomer (-)-**6**, $[\alpha]_D$ -136.1 (c = 1.00, $CHCl_3$) and the trifluoroethoxy derivative **7**. The spirodienone intermediate **8** was not isolated but h.p.l.c. analysis indicated that after $^1/_2$ hour this was the major product formed (Scheme 2).



Scheme 1

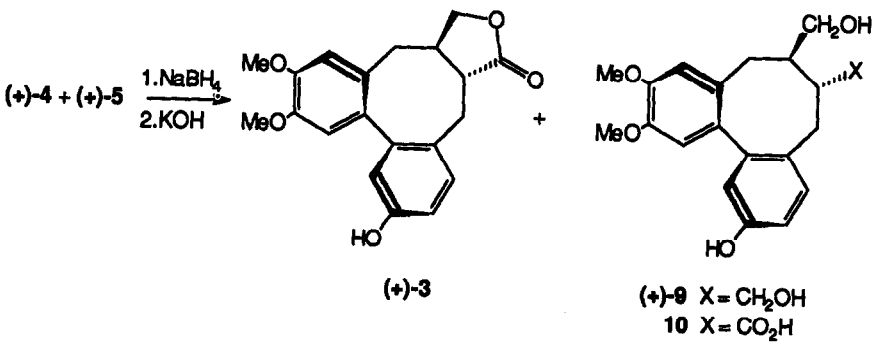
The structures of (+)-**4**, (+)-**5** and (-)-**6** were based on an analysis of their ^{1}H and ^{13}C n.m.r. spectra and in particular upon comparison with the spectra of similar racemic compounds lacking only the menthyloxy substituent.[3,4] Thus the isostegane derivatives (+)-**4** and (+)-**5** showed characteristic signals in their ^{13}C n.m.r. spectra at 46.5 and 50.5, and 47.6 and 50.8 p.p.m., respectively, due to C-6 and C-7, while compound (-)-**6** had corresponding signals at 41.9 and 47.5 p.p.m. characteristic of the stegane series.[5,6] That **4** and **5** only differed in their configuration at C-13 was evident from their ^{1}H n.m.r. spectra, which differed only in that they contained doublets at δ5.2 (J = 4.7) and 5.5 (J = 8.2) respectively.

It is assumed that epimerisation at C-13 is brought about by trifluoroacetic acid formed during the reaction. It is of interest to note that both (+)-**4** and (+)-**5** arise from an aryl migration from the spirodienone **8**, in line with our previous experience using related compounds.[3]



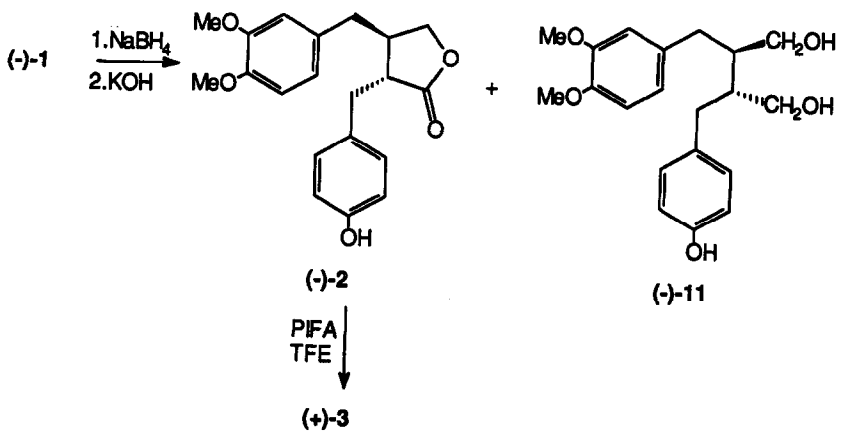
Scheme 2

Treatment of a mixture of (+)-**4** and (+)-**5** with $NaBH_4$ and KOH[4] gave as a major product (+)-**3** (37%), $[\alpha]_D$ + 108.8 (c = 0.25, $CHCl_3$) in which the menthyloxy group has been removed, along with smaller amounts of the diol (+)-**9** (28%) $[\alpha]_D$ + 63.2 (c = 0.25, EtOH) and the hydroxy acid **10** (22%). When compound **10** was left in a dessicator over P_2O_5 it was slowly and quantitatively transformed into the lactone (+)-**3** (Scheme 3). Thus the overall yield of (+)-**3** from **4** and **5** was 59%. The structure of (+)-**3** was firmly established by comparison of its ^1H and ^{13}C n.m.r. spectra with those of the corresponding racemic compound.[3]



Scheme 3

Finally, treatment of the dibenzylbutyrolactone **1** with $NaBH_4$ and KOH, gave as the major product (-)-**2**, $[\alpha]_D$ - 29.5 (c = 0.27, $CHCl_3$) (43%) along with 11% of the diol (+)-**11**, $[\alpha]_D$ - 32.1 (c = 0.14, $CHCl_3$). Treatment of (-)-2 with PIFA in TFE gave once again the isostegane (+)-**3**, identified by h.p.l.c. comparison with the sample prepared from (+)-**4** and (+)-**5** (Scheme 4).



Scheme 4

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