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# SYNTHETIC METHODOLOGY FOR THE PREPARATION OF *TRANS*- AND *CIS*-2,9-DISUBSTITUTED OXONANES.

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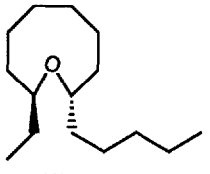
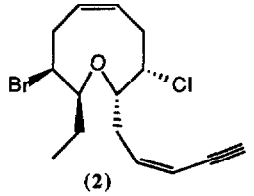
*Summary*: Methylenation of the racemic lactone (**5**), followed by stereoselective hydroboration, gave predominantly the *trans*-2,9-disubstituted oxonane (**7**) which was converted into the carbon skeleton (**1**) of obtusenyne (**2**). Epimerisation of the *trans*-aldehyde (**18**) gave the *cis*-compound (**19**). Relative stereochemistry was established by the asymmetric synthesis of *trans*-(2*R*),(9*R*)-dimethyloxonane (**13**) and *meso cis*-2,9-dimethyloxonane (**17**).

Recent isolation of biologically active marine natural products having medium ring ether functionality,[1] predominantly from various *Laurencia* species, has stimulated great interest in developing synthetic methodology for these challenging targets.[2] We have previously reported an approach to the most common oxocane ring size.[3,4] This Letter describes extension of the methodology to the nine-membered, oxonane, ring system having either *trans*- or *cis*-2,9-disubstitution and is illustrated by the synthesis of (**1**), corresponding to the carbon skeleton of the *Laurencia* natural product obtusenyne (**2**).[5]



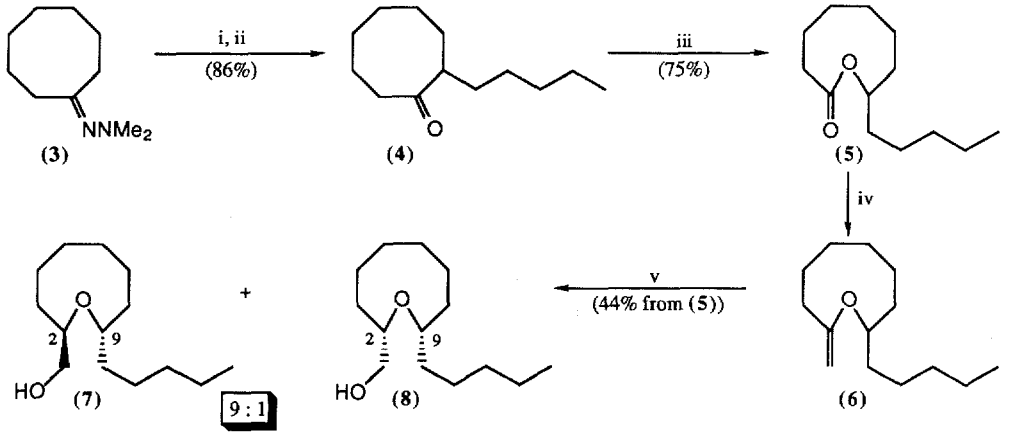

(1)




(2)

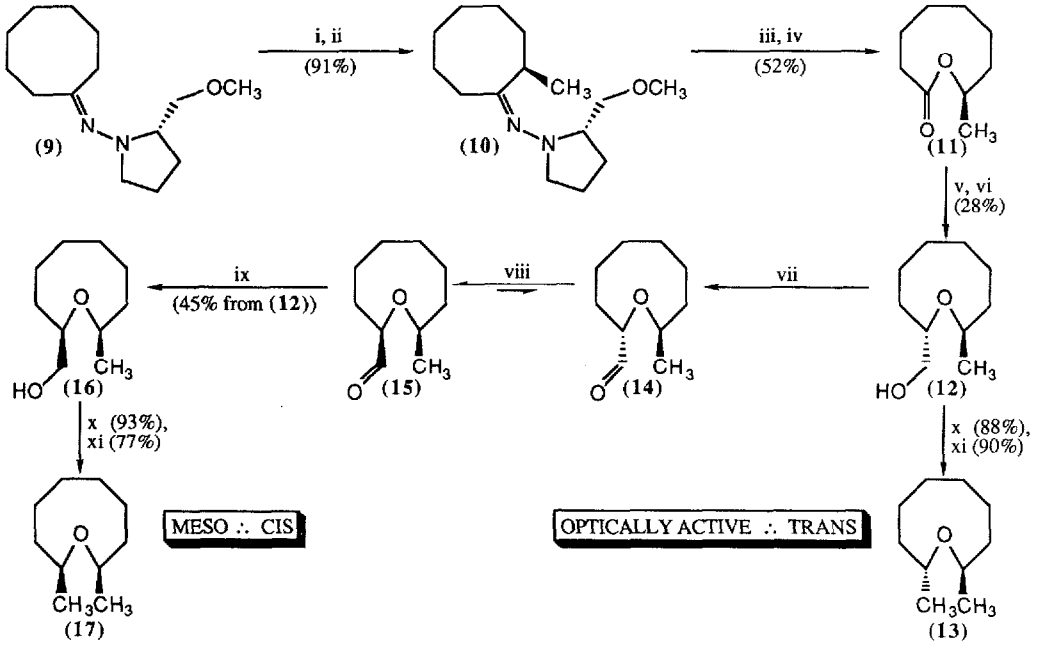
The racemic substituted octanolide (**5**)[6] was obtained by Baeyer-Villiger oxidation[7] of the ketone (**4**),[6] available by alkylation of the dimethyl hydrazone (**3**)[8] (Scheme 1). Methylenation of this lactone with the Tebbe reagent[9] afforded the labile enol ether (**6**) which was immediately hydroborated with borane-THF complex. Oxidation of the resulting organoborane yielded a 9:1 ratio of *trans*, (**7**),[6] and *cis*, (**8**),[6] oxonane alcohols, separable by chromatography. By-products resulting from elimination of the intermediate organoborane were also isolated.

**SCHEME 1**




Reagents: i, BuLi, THF, -78°C then $C_5H_{11}I$; ii, 10% aq. $H_2SO_4$; iii, $CF_3CO_3H$, $Na_2HPO_4$, $CH_2Cl_2$; iv, $(C_5H_5)_2Ti(\mu\text{-}CH_2,\mu\text{-}Cl)AlMe_2$, DMAP, THF, toluene, -40° to 25°C then NaOH, -15° to 25°C; v, $BH_3$-THF, THF, 0°C then NaOH, $H_2O_2$, 0°C.

**SCHEME 2**

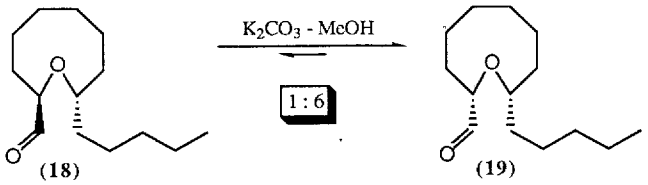



Reagents: i, LDA, THF, 0°C, 15h; ii, MeI, -95°C; iii, $O_3$, $CH_2Cl_2$, -78°C; iv, $CF_3CO_3H$, $Na_2HPO_4$, $CH_2Cl_2$; v, $(C_5H_5)_2Ti(\mu\text{-}CH_2,\mu\text{-}Cl)AlMe_2$, DMAP, THF, toluene, -40° to 25°C then NaOH, -15° to 25°C; vi, $BH_3$-DMS, THF, 0°C then NaOH, $H_2O_2$, 0°C; vii, PCC, $CH_2Cl_2$; viii, $K_2CO_3$, MeOH, 3d; ix, $NaBH_4$; x, TsCl, DMAP, $CH_2Cl_2$; xi, $LiAlH_4$, ether.

The presence of an nOe between $H_2$ and $H_9$ in the 3,5-dinitrobenzoate of (**8**), and no such effect in the corresponding derivative of (**7**), supported the assigned relative stereochemistry. However, limited information about nine-membered ring conformations precluded unequivocal assignment. Furthermore, the apparent contrast between *trans*-selective hydroboration of (**6**) and the corresponding preference for *cis*-compounds in the oxocane[3,4,10] and oxepane[11] series demanded proof of relative stereochemistry.

In order to establish unambiguously the validity of the assigned relative stereochemistry, asymmetric synthesis of *trans*-(2*R*),(9*R*)-dimethyloxonane (**13**) and *meso cis*-2,9-dimethyloxonane (**17**) was undertaken (Scheme 2).[13]

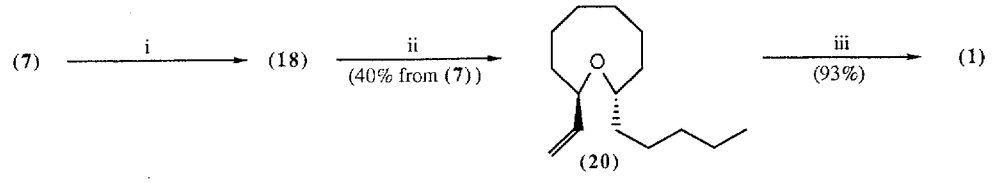
Ozonolysis followed by Baeyer-Villiger oxidation[14] of SAMP-hydrazone (**10**)[15] gave octanolide (**11**)[6] {$[\alpha]_D$ -41° (*c* 1.0, MeOH)} in 91% e.e.[16] Methylenation followed by hydroboration-oxidation gave a single oxonane product (**12**)[6] {$[\alpha]_D$ -23° (*c* 1.1, $CHCl_3$)}. This was converted into the corresponding tosylate then reduced to give *trans*-(2*R*),(9*R*)-dimethyloxonane (**13**)[6] {$[\alpha]_D$ -50° (*c* 0.51, $CDCl_3$)}. The *cis*-oxonane alcohol (**16**)[6] {$[\alpha]_D$ -16° (*c* 0.6, $CHCl_3$)} was available from (**12**) by oxidation to the aldehyde, base-catalysed epimerisation, and reduction [49:1 ratio of (**16**):(**12**) by G.C.]. Conversion by the same sequence as before gave *cis*-2,9-dimethyloxonane (**17**)[6] {$[\alpha]_D$ 0° (*c* 0.59, $CDCl_3$)}.[17] This confirmed that the major product from the methylenation-hydroboration sequence on a 9-substituted octanolide did indeed have *trans* relative stereochemistry.




Base-catalysed equilibration of the racemic aldehyde (**18**) favoured (6:1) the *cis*-product (**19**). Thus, a versatile strategy for synthesis of both *trans* and *cis*-2,9-disubstituted oxonanes has been developed.

Synthesis of the carbon skeleton (**1**) of obtusenyne (**2**) from the alcohol (**7**) was achieved as outlined in Scheme 3. Oxidation followed by Wittig homologation gave the alkene (**20**),[6] which was hydrogenated to give *trans*-2-ethyl-9-pentyloxonane (**1**).[6]

**SCHEME 3**




Reagents : i, PCC, $CH_2Cl_2$; ii, $Ph_3P{=}CH_2$, THF; iii, $H_2$, Pd-C, EtOAc.

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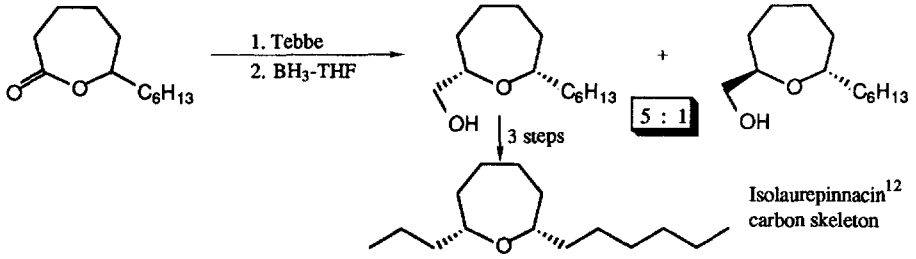


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17. In addition, [α] 0° at λ 578, 546, 436, and 365nm.

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