SYNTHETIC STUDIES ON CLERODANE DITERPENOIDS. 3. AN ALTERNATIVE SYNTHESIS OF AN UNNATURAL ANTIFEEDANT[1,2]

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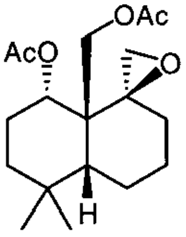
Abstract – An alternative synthesis of (1S*,2S*,6R*,10S*)-2-acetoxy-1-acetoxymethyl-5,5-dimethylbicyclo[4.4.0]decane-10-spiro-2'-oxirane (**1**), an unnatural antifeedant, has been effected *via* an intermolecular Diels-Alder approach.

During the investigation of clerodane diterpenoids, Ley *et al.*[3] observed that (1S*,2S*,6R*,10S*)-2-acetoxy-1-acetoxymethyl-5,5-dimethylbicyclo[4.4.0]decane-10-spiro-2'-oxirane (**1**), a simple analogue of the natural antifeedant clerodin,[4] also showed interesting insect antifeedant activity. They prepared this compound in eight synthetic operations starting from 4,4-dimethyl-2-cyclohexenone.[3] We wish to report herein an alternative synthesis of this unnatural antifeedant.



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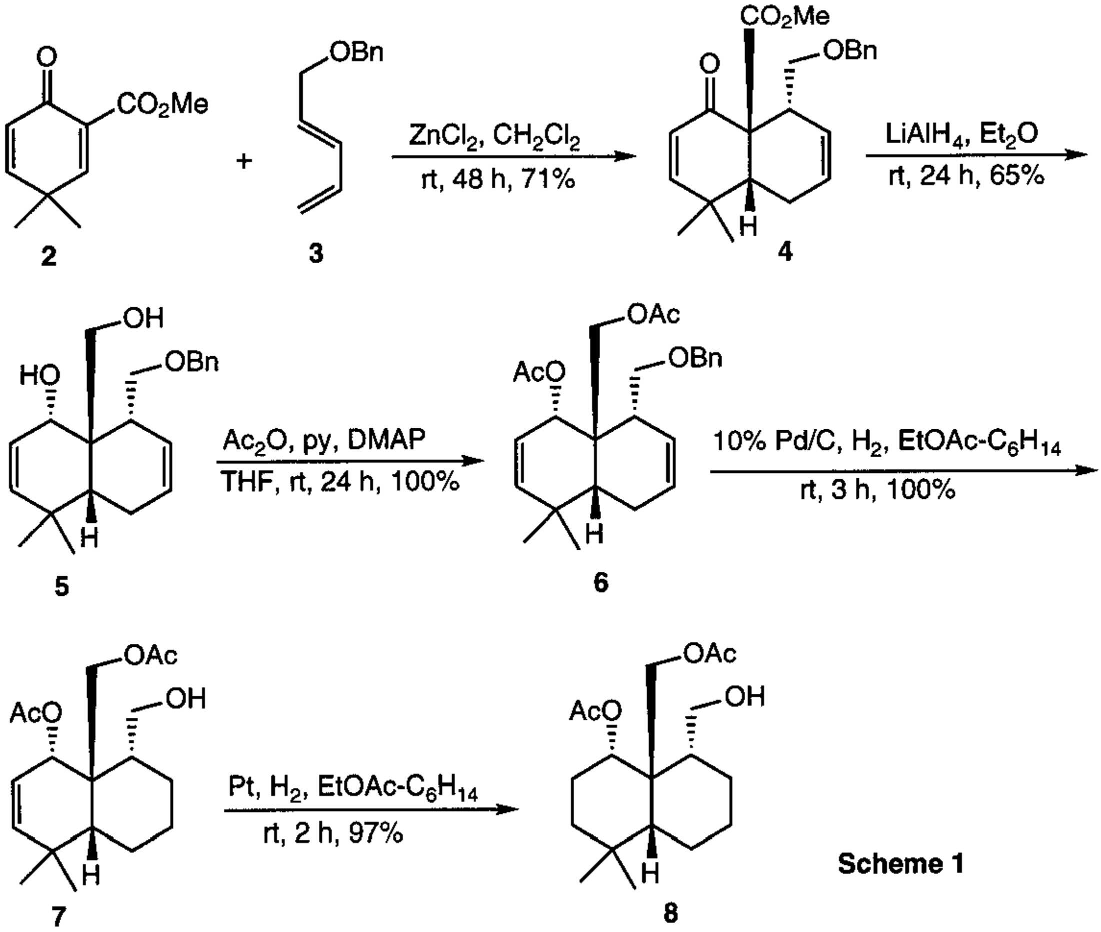
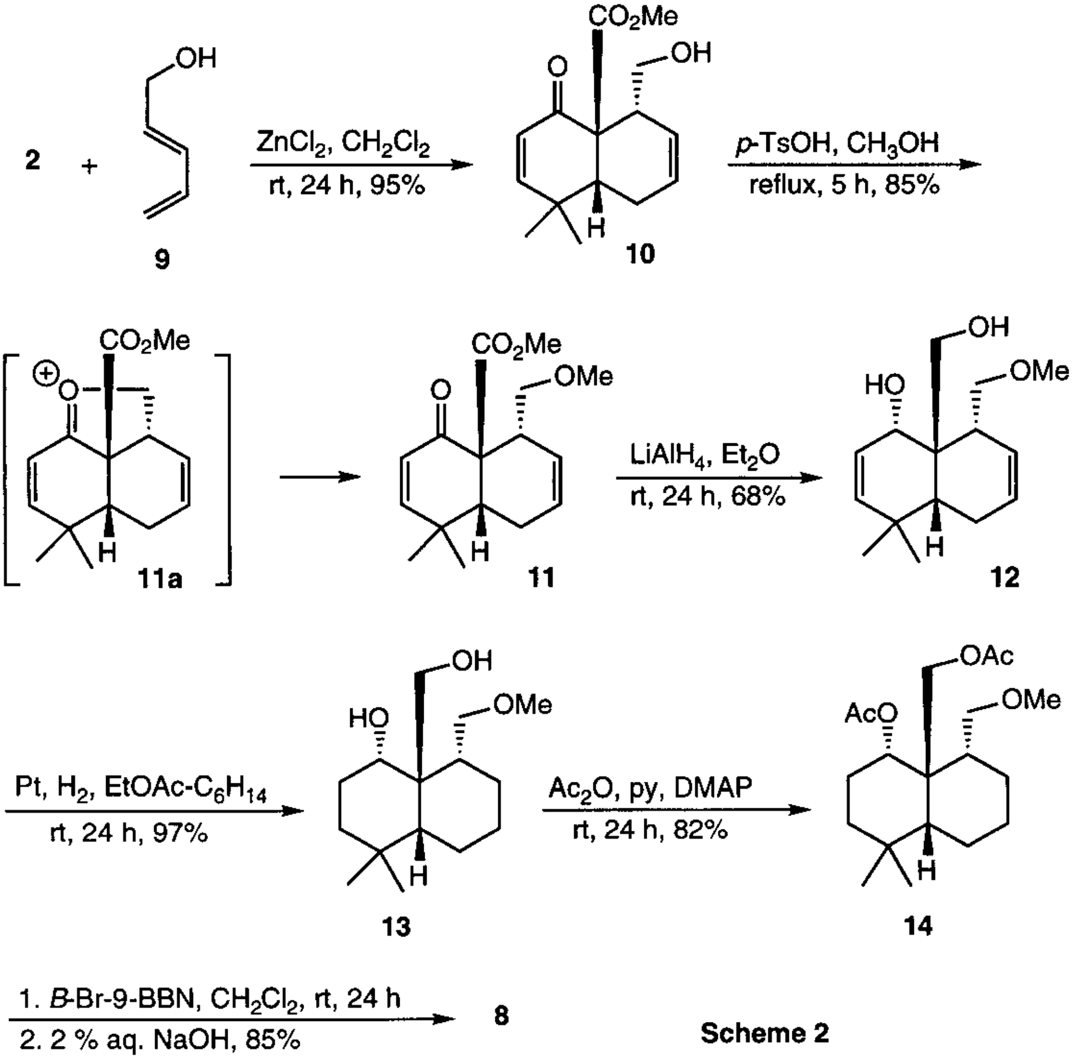
Our approach to the requisite *cis*-decalin system possessing appropriate oxidation level at various key centers was based on an intermolecular Diels-Alder reaction. This was effected by the addition of dienone ester (**2**)[5] to diene (**3**).[6] Under zinc chloride catalysis the reaction occurred readily and efficiently. After 48 h at room temperature in methylene chloride using one part each of the diene and dienophile, adduct (**4**) was isolated in 71% yield. Subsequent reduction of adduct (**4**) with lithium aluminum hydride gave a 65% yield of the desired diol (**5**) which was acetylated with acetic anhydride in tetrahydrofuran in the presence of pyridine and 4-dimethylaminopyridine. Diacetate (**6**) thus obtained in quantitative yield was subjected to debenzylation with 10% palladium on carbon under an atmosphere of hydrogen.[8,9] Further hydrogenation of the resulting alcohol (**7**) using platinum as a catalyst resulted in the formation of the corresponding saturated alcohol (**8**) in 97% yield over two steps.



Scheme 1

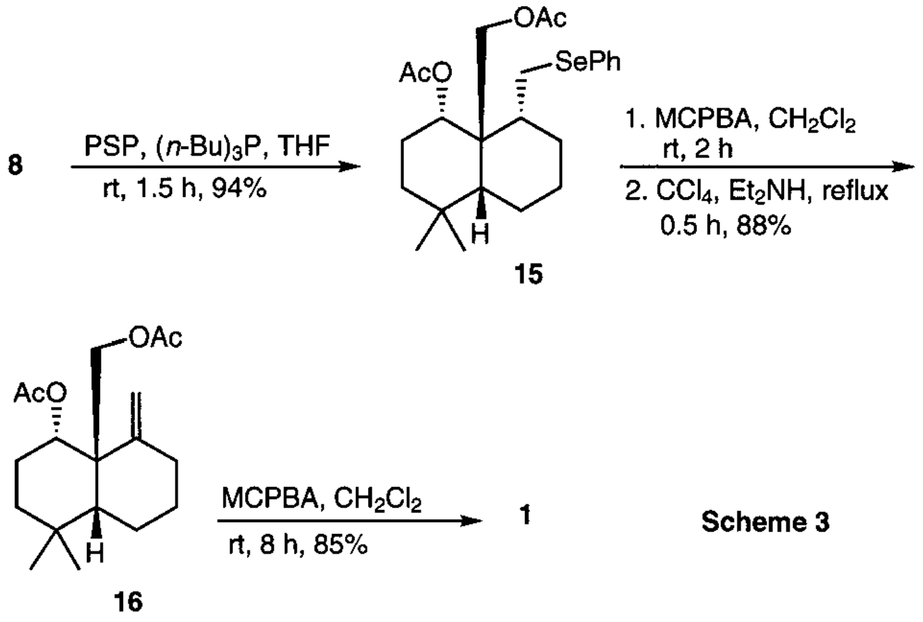
An alternative approach to this key intermediate (**8**) has also been developed (Scheme 2). In this approach, 2,4-pentadienol (**9**)[6] was used as the diene in the initial Diels-Alder reaction. Its addition to dienone (**2**) under zinc chloride catalysis gave adduct (**10**) in nearly quantitative yield. Interestingly, when compound (**10**) was treated with a trace amount of *p*-toluenesulfonic acid in refluxing methanol, the corresponding methyl ether (**11**) was formed in 85% yield, presumably *via* the intermediacy of oxonium ion (**11a**). Reduction of **11** with



Scheme 2

lithium aluminum hydride followed by catalytic hydrogenation of the resulting diol (**12**) using platinum gave rise to saturated diol (**13**) (66% overall yield). Diol (**13**) was acetylated with acetic anhydride in pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine to give the corresponding diacetate (**14**) (82% yield) which was subjected to demethylation with *B*-bromo-9-borobicyclo[3.3.1]nonane[10] followed by brief treatment with aqueous sodium hydroxide to furnish the desired alcohol (**8**) (85% yield).

The conversion of alcohol (**8**) to the target compound (**1**) was carried out as follows (Scheme 3). Treatment of **8** with *tri-n*-butylphosphine and *N*-(phenylseleneno)phthalimide (PSP)[11] in tetrahydrofuran effected the replacement of its hydroxy group with a phenylseleneno group, enroute to the installation of the required double bond. Subsequent oxidation of the resulting selenide (**15**) (94% yield) using *m*-chloroperbenzoic acid followed by an elimination reaction carried out in refluxing carbon tetrachloride containing a small amount of diethylamine gave rise to the desired olefin (**16**). Finally, epoxidation of **16** with *m*-chloroperbenzoic acid furnished the target compound (**1**), of which the spectroscopic data were found to be in good agreement with those reported.[3] In addition to providing an effective alternative synthesis of an interesting insect antifeedant, the current work also served as a model study for the construction of clerodin and related clerodane diterpenoids.



Scheme 3

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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