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Use of *cis*-3-Cyclobutene-1,2-dimethanol in Stereoselective Routes to some Naturally Occurring Conjugated Dienes and Trienes

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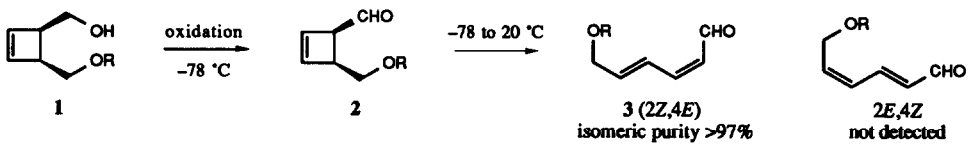
Abstract: Thermal electrocyclic ring-opening of 4-alkyl-2-cyclobutene-1-carbaldehydes occurs at low temperature to give (2*Z*,4*E*)-alka-2,4-dienals exclusively, and this process is exploited *en route* to various isomeric naturally occurring 1,3,5-alkatrienes and 2,4-decadienoates from a single precursor, *cis*-3-cyclobutene-1,2-dimethanol **4**.

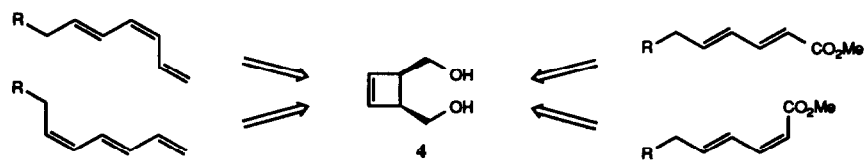
The thermal electrocyclic ring-opening of a cyclobutene is a process with considerable potential in conjugated diene synthesis,[2] but its value as a source of single geometric isomers was for a long time obscured by the ambiguity of the symmetry-based selection rule, which defines two 'allowed' modes of conrotatory ring-opening for substituted systems. For example, heating an unsymmetrical *cis*-1,4-disubstituted 2-cyclobutene can in principle give two isomeric (*Z*,*E*)-dienes.[3] However, there is now compelling evidence that stereoselection during cyclobutene ring-opening is dominated by the electronic effects of the allylic substituents, with π-donors preferring 'outward' conrotation, and π-acceptors more readily undergoing the alternative 'inward' motion.[4-6] In this context we originally showed that Swern oxidation of **1** gives a cyclobutene **2** whose allylic substituents (formyl, alkoxyalkyl) have complementary conrotation preferences, and which consequently undergoes thermal electrocyclic ring-opening to give the (*Z*,*E*)-dienal **3** stereoselectively and at low temperature (Scheme 1).[4,7]



1 **2** **3** (2*Z*,4*E*) isomeric purity >97% 2*E*,4*Z* not detected

SCHEME 1 (R = 4-MeOC$_6$H$_4$CH$_2$)

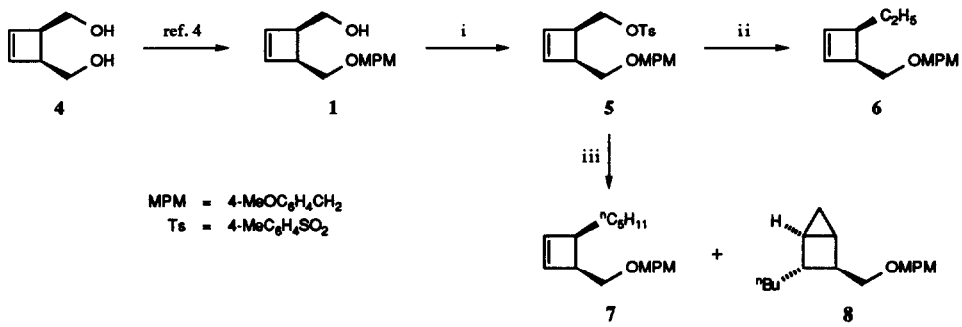
We now wish to describe how the above principle can be exploited in approaches to some naturally occurring conjugated dienes and trienes, each derived with high and predictable isomeric purity from the same precursor, *cis*-2-cyclobutene-1,4-dimethanol **4**, a distillable liquid of considerable versatility in diene synthesis.



4

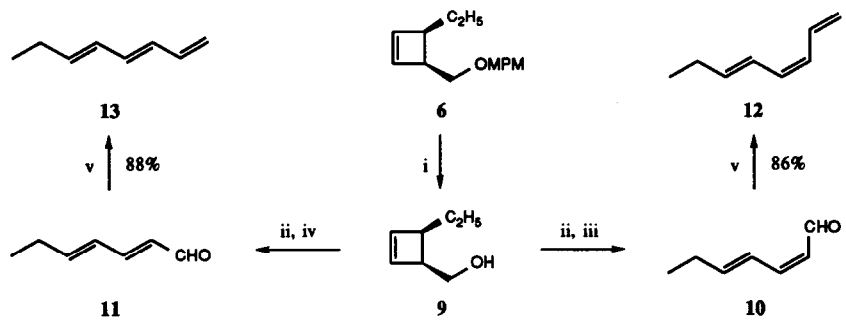
The R-substituent to be located at the (*E*)-terminus of each (*Z*,*E*)-diene fragment is introduced at the cyclobutene stage, prior to the stereoselective ring-opening reaction. The *p*-methoxybenzyl ether **1**, obtained

from the diol **4** as described,[4] is first transformed into the tosylate **5** and then treated with the appropriate cuprate reagent (Scheme 2). Using lithium dimethylcuprate thus provided the ethyl-substituted cyclobutene **6**, whereas the *n*-butyl reagent afforded **7**, accompanied by varying amounts of a by-product, the bicyclo[2.1.0]pentane **8**.[8]



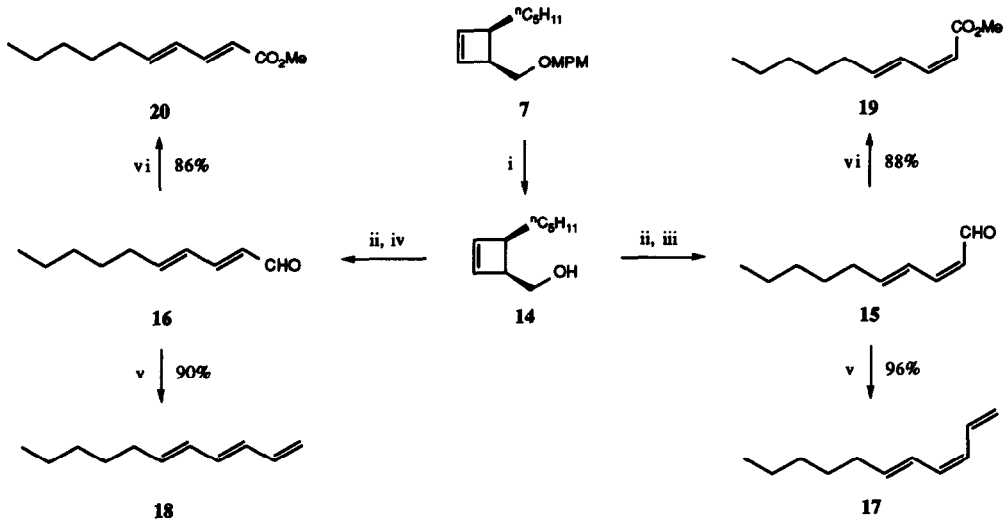
SCHEME 2 *Reagents:* i, *n*-BuLi, THF-hexane, *p*-$MeC_6H_4SO_2Cl$, –78 to 20 °C (83%); ii, Me_2CuLi, Et_2O, –10 to 0 °C (78%); iii, *n*-Bu_2CuLi, Et_2O-hexane, –10 to 0 °C (75% of **7**; ≤15% of **8**).

Deprotection of the ether **6** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] gave the alcohol **9**, which was transformed into the (*Z*,*E*)-dienal **10** *via* Swern oxidation at –78 °C (Scheme 3). Florisil chromatography was used to isolate **10** with high (>97%)[10] isomeric purity, otherwise the product was accompanied by trace amounts of the more stable (*E*,*E*)-isomer **11**, which could be obtained pure by quenching the oxidation at 20 °C and isolating the product by flash silica chromatography. Wittig methylenation was used to convert the dienals **10** and **11** into the respective (3*Z*,5*E*)- and (3*E*,5*E*)-1,3,5-octatrienes **12** and **13**, which are components of the female sex attractant of the brown seaweed *Fucus serratus*.[11,12]



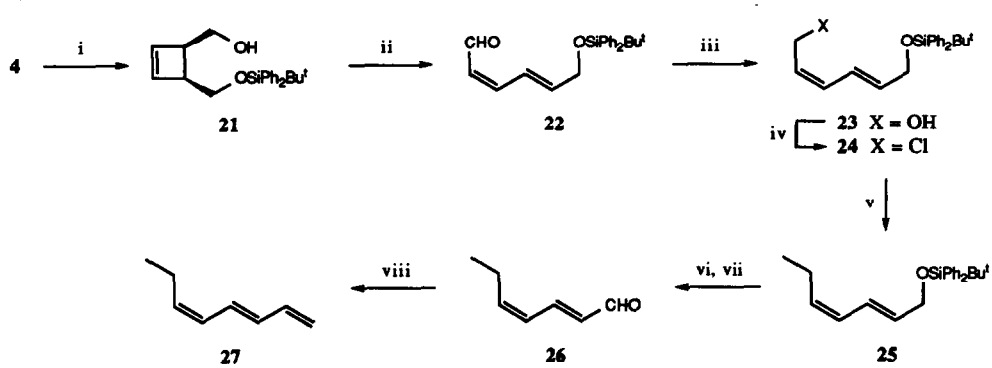
SCHEME 3 *Reagents:* i, DDQ, CH_2Cl_2–H_2O, 20 °C, 2 h (91%); ii, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 1 h; iii, Et_3N, –78 to 20 °C, Florisil column (92%); iv, –78 to 20 °C, then Et_3N, flash silica column (87%); v, $Ph_3P{=}CH_2$, THF, 0 to 20 °C.

Following the protocol outlined above, the *n*-pentyl cyclobutene **7** was transformed into the alcohol **14**, and hence the isomeric dienals **15** and **16** (Scheme 4). Methylenation of these gave the 1,3,5-undecatrienes **17** and **18**, which occur naturally in the essential oil of galbanum (*Ferula galbaniflua*)[13] and the Hawaiian seaweed *Dictyopteris plagiogramma*.[14] The pure (3*E*,5*Z*)-isomer **17** is valued as a fragrance in the perfume industry.[15] Treatment of the dienals **15** and **16** with manganese(IV) oxide and sodium cyanide in methanol[16] gave the methyl decadienoates **19** and **20**. The (2*Z*,4*E*)-isomer **19**[17] is a pheromone component of the forest pest *Pityogenes chalcographus*,[17a] and a component of stillingia oil, obtained from the seeds of *Sapium sebiferum*, the Chinese tallow tree.[18] Methyl (2*E*,4*E*)-decadienoate **20** is a component of the flavour principles of the Bartlett pear.[19]



SCHEME 4 *Reagents:* i, DDQ, CH_2Cl_2–H_2O, 20 °C, 2 h (79%); ii, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 1 h; iii, Et_3N, –78 to 20 °C, Florisil column (83%); iv, –78 to 20 °C, then Et_3N, flash silica column (90%); v, $Ph_3P{=}CH_2$, THF, 0 to 20 °C; vi, MnO_2, NaCN, MeOH.

Since the formyl substituent is a crucial (*Z*)-selective control element in the thermal ring-opening of a 2-cyclobutene-1-carbaldehyde, any substituent to be located on the (*Z*)-terminus of a (*Z*,*E*)-diene fragment must be introduced after the stereoselective ring-opening process. To allow for mild deprotection at the diene stage the diol **4** was monosilylated[20] to obtain the cyclobutenemethanol **21**, and the latter proved to be a suitable starting point for (2*E*,4*Z*)-dienal preparation as illustrated in Scheme 5. Swern oxidation of **21** gave the (2*Z*,4*E*)-dienal **22**, which was immediately transformed into the alcohol **23**[21] and hence[22] the chloride **24**. Treating the latter with methyl Grignard reagent gave mainly the S_N2 displacement product **25**, which was isolated by flash chromatography over silica gel. Desilylation, followed by oxidation using tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[23] yielded the (2*E*,4*Z*)-dienal **26**, which on methylenation gave (3*E*,5*Z*)-octatriene **27**, the remaining isomer of the mixture found in the seaweed *Fucus serratus*.[11]



SCHEME 5 *Reagents:* i, NaH, THF, *t*-$BuPh_2SiCl$, (93%); ii, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 2 h, Et_3N, –78 to 20 °C, Florisil column (83%); iii, $LiBH_4$, THF (78%); iv, $MeSO_2Cl$, LiCl, collidine, DMF, 0 to 20 °C (86%); v, MeMgBr, toluene-THF (79%); vi, *n*Bu_4NF, THF (91%); vii, TPAP, NMO, 4Å sieves, CH_2Cl_2, 20 °C (73%); viii, $Ph_3P{=}CH_2$, THF, 0 to 20 °C (>85%).

Extensions of the principle embodied in the above results, *i.e.* that high stereoselectivity in the thermal ring-opening of *cis*-1,4-disubstituted 2-cyclobutenes can be ensured by arranging that the substituents have complementary conrotatory preferences, are currently under investigation and will be described in due course.

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10 All isolated yields refer to material of at least 95% isomeric purity, as estimated by 300 MHz ^{1}H n.m.r. spectroscopy. The (2*Z*,4*E*)-dienals [δ *ca.* 10.2 ppm, C<u>H</u>O] were the only (*Z*,*E*)-isomers detected in the ring-opened products. Isomerisation to the more stable (2*E*,4*E*)-isomers [δ *ca.* 9.5 ppm, C<u>H</u>O], especially in the presence of acid, appeared to be the only source of contamination. The (2*Z*,4*E*)-dienals were therefore used without delay.

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