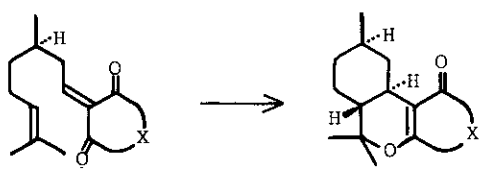
STEREOSELECTIVE FORMATION OF A CYCLOPENTANOID WITH THREE CONTIGUOUS SUBSTITUENTS VIA INTRAMOLECULAR CYCLOADDITION

Seiichi Takano,* Shigeki Satoh, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract ——A stereoselective formation of a cyclopentanoid with three contiguous substituents has been demonstrated by using a linear aldehyde and Meldrum's acid via an intramolecular cycloaddition.

Stereoselectivity in the intramolecular cycloaddition of a certain electron deficient heterodiene system has been well established by Tietze and co-workers using the substrates such as 1 which afford dihydropyran derivatives with cyclohexane ring in highly stereoselective fashion[1-4] (Scheme 1). In relation to synthetic studies of natural products containing cyclopentane framework[5-8] we tried to apply this intramolecular cycloaddition reaction to the construction of cyclopentanoids with three contiguous substituents via the formation of a dihydropyran derivative with an appropriately substituted cyclopentane system by reducing one carbon unit between a diene and a dienophile as the pyran system can be regarded as two contiguous



1 2

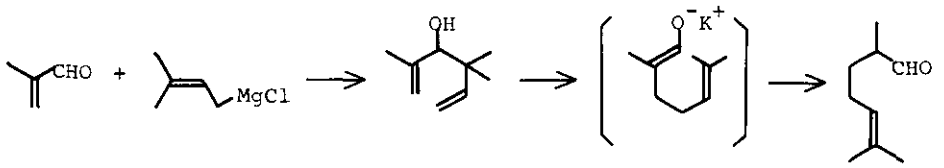
X=-$(CH_2)_3$-
or
-$CH_2CH(C_5H_{11}{}^n)CH_2$-
or
-$OC(Me)_2O$-
or
-NHCONH-
or
-NMeCONMe-

Scheme 1

substituents. In order to test the feasibility of our intention we examined the intramolecular cycloaddition of the heterodiene system (9) generated from 2,6-dimethyl-5-heptenal (7) and Meldrum's acid (8). Preparation of 2,6-dimethyl-5-heptenal (7) was accomplished in two steps in an efficient manner starting from methacrolein (3) and prenyl chloride via regioselective Grignard addition followed by oxy-Cope rearrangement. Thus, methacrolein (3) was reacted with prenylmagnesium chloride (2) prepared in situ

from prenyl chloride exclusively at allylic position of the Grignard compound to give 2,4,4-trimethyl-1,5-hexadien-3-ol (5) in 77% yield as a sole product. The observed regioselectivity could not be altered even by addition of copper catalyst.[9-12] Conversion of the dienol (5) into 2,6-dimethyl-5-heptenal (7) was carried out easily in 91% yield by treating with potassium hydride (2.0 mol. equiv.)[13] in refluxing tetrahydrofuran for 1 h.

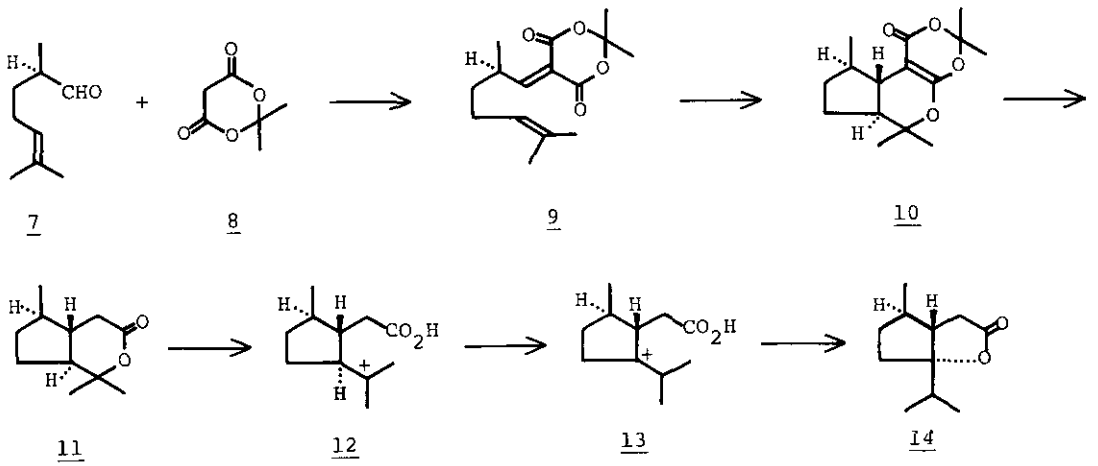
Treatment of the heptenal (7) with Meldrum's acid (8) (1.2 mol. equiv.) in isopropylalcohol in the presence of ethylenediammonium acetate[14] (4 mol. % equiv.) at room temperature furnished the tricyclic adduct (10) as a single product, via concurrent aldolization and intramolecular cycloaddition, which could be used without further purification in the next reaction. No trace of the aldolization product (9) could be detected in the reaction mixture (Scheme 2).



3 4 5 6 7

Scheme 2

To delineate the stereochemistry of the adduct (10), we next attempt to convert 10 into the known cyclopentanoid (20) with three contiguous substituents whose all stereoisomers have been already known.[15] Thus, 10 was refluxed in water for 11 h to give the bicyclic -lactone (11) in 46% yield via concomitant deacetonylation and decarboxylation. When 10 was refluxed with diluted acid (20% HCl in THF 2 : 1), further acid catalyzed reaction took place to generate the rearranged product (14) presumably via the cationic intermediates (12) and (13) (Scheme 3).

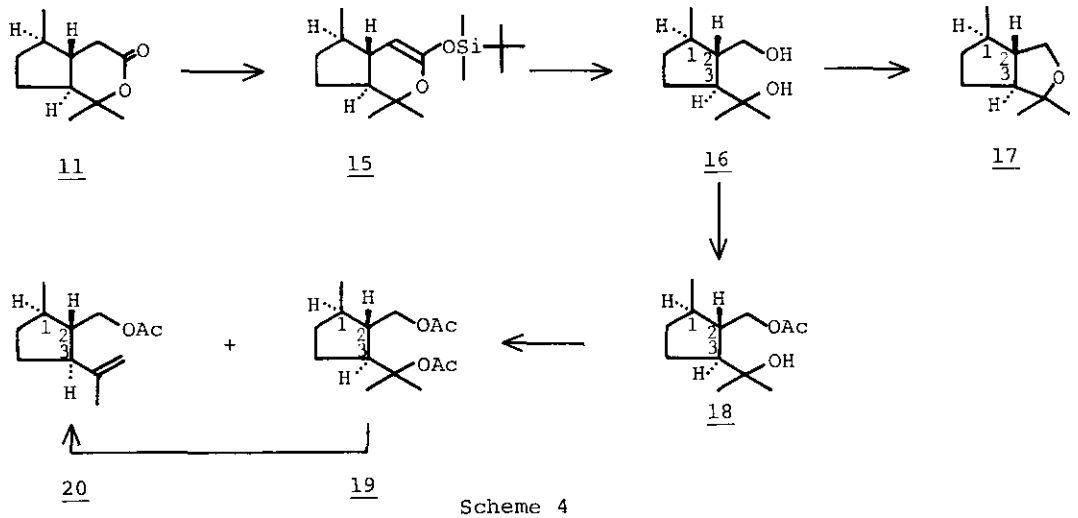


7 8 9 10

11 12 13 14

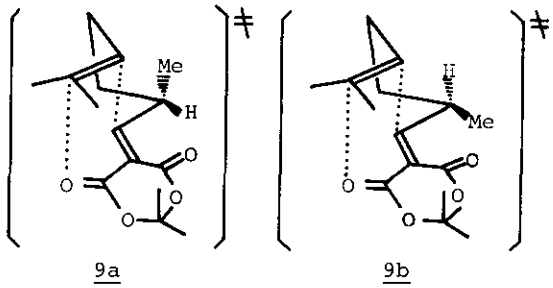
Scheme 3

The δ-lactone (11) was then transformed to the silyl enolate (15), by employing standard conditions,[16] which was sequentially ozonized (-78 °C) and reduced ($NaBH_4$, 0 °C - room temperature) in methanol in the same flask to give the diol (16) in 43% overall yield. This compound did not give the five membered ether (17) under the same conditions which the cis-(2,3)-isomer of 17 does cyclize.[17,18] The trans ether (17) could be eventually obtained in 44% yield by treating 16 sequentially with n-butyllithium (1.1 mol. equiv.), p-toluenesulfonyl chloride (1.1 mol. equiv.), and n-butyllithium (1.1 mol. equiv.) in tetrahydrofuran at -78 °C.[19] Its spectral data (I.R. and ^{1}H-N.M.R.) were not identical with those of both the



Scheme 4

cis-(2,3)-isomers of 17 kindly provided by Professor Yamada.[20] The trans ether (17) was found to be very unstable presumably owing to its strained bicyclic structure and was decomposed gradually on standing at room temperature. Total stereochemistry of 16 was unambiguously confirmed to be trans-trans-(1,2 : 2,3)-configuration by converting it into the known compound (20).[15] Thus, on acetylation with acetic anhydride in methylene chloride in the presence of pyridine at room temperature 16 gave the monoacetate (18), excellently, which on further treatment with hot acetic anhydride furnished the diacetate (19) and the known trans-trans olefin (20).[15] The former compound (19) could also be converted to the latter olefin (20) upon pyrolysis at 180 °C in a sealed capillary (Scheme 4).



Scheme 5

These results conclude us that the intramolecular cycloaddition of the transient intermediate (9) generated from 2,6-dimethyl-5-heptenal (7) and Meldrum's acid (8) proceeded with highly stereoselective manner by the effect of the allylic methyl group which directs to take the conformer 9a rather than 9b in the transition state to give rise the one isomer (10) (Scheme 5). We have now engaged in the synthesis of cyclopentanoid natural products exploiting the present findings.

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