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Novel Synthesis of Trioxatetracyclo[5.3.2.0.^{4,9}.0^{4,11}]dodecane and Bibenzyl Skeletons

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***Abstract**: A novel 7, 9, 11-trimethyl-8,10,12-trioxatetracyclo[5.3.2.0.^{4,9}.0 ^{4,11}]-dodec-1-yl]-2-butanone skeleton **3** has been synthesized by the treatment of 2-acetyl-3,4-dihydro-2,5-di (3''-oxo-butyl)-6-methyl-(2H)-pyran **2**, with H-ZSM-5. However,the treatment of compound 2 with p-TsOH gives bibenzyls. Present report provides a unique acid catalysed cyclization of diketo-olefin system over zeolite, X-ray crystal structure of 3 is also presented.*

The last decade has witnessed considerable resurgence of interest in the area of zeolite induced organic transformations.[1] Acidic zeolites are in the increasing demand for selectivity, efficiency, easy work up and effluent pollution control.

Spiroketals and related oxygen heterocycles enjoy widespread occurrence[2-8] as substructures of naturally occurring molecules from many sources including microbes, plants, fungi, insects and marine organisms. They have adopted an important role in a host of biologically active natural products notably insect pheromones, polyether antibiotics, antiparasitic, antiinflammatory, antitumour, hypocholesterolemic agents.[2,3] The increasing pharmacological and agrochemical importance of these compounds has triggered intense interest in both their synthesis and chemical reactivity. Although several strategies have been employed for their synthesis, the acid catalysed cyclization of dihydroxy olefins,[9] hydroxy diketones,[4,10] or

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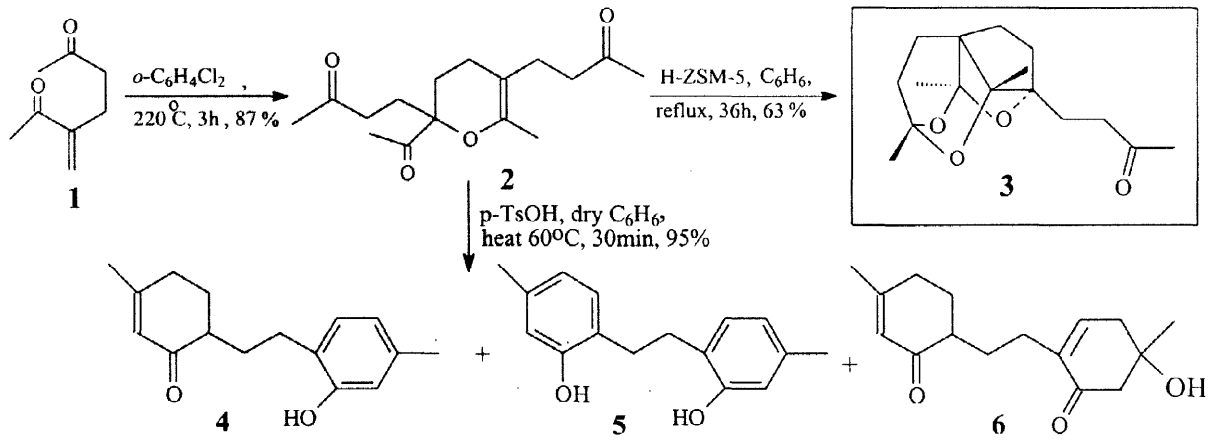
an equivalent there of is the predominant ring forming process. Many bibenzyls have been found in the hepaticae[11] and their preparation is of current interest.

We report herein facile formation of 7, 9, 11-trimethyl-8, 10, 12-trioxatetracyclo[5.3.2.0.^{4,9}.0 ^{4,11}]-dodec-1-yl]-2-butanone (3) from tricarbonyl dihydropyran derivative 2 over H-ZSM-5. The acid form of zeolite Na-ZSM-5 (Si/Al=65) was obtained through successive ion-exchange with 1M NH_4NO_3 solution (3 times) and subsequent heating at 673K for 6h.



Scheme-1

The treatment of methyl vinyl ketone with DABCO yielded the dimer **1**,[12] which underwent hetero-Diels-Alder reaction[13] in refluxing o-dichlorobenzene to give 2-acetyl-3, 4-dihydro-2, 5-di (3'-oxo-butyl)-6-methyl-(2H)-pyran (**2**).[14] The treatment of compound **2** (0.98g, 7mmol) with zeolite (0.4g) in refluxing benzene (8ml) for 36 h yielded a novel spiroketal **3**[15] (63%) (scheme-1). For comparison, the compound **2** was heated in the presence of p-TsOH (120mg) in benzene (8ml) at 60°C for 30min which yielded compounds 3-methyl-6-[2(4'-methyl-2'-hydroxy)phenyl]-ethyl-cyclohexa-2-en-1-one (**4**, 58%), 2, 2' - dihydroxy - 4, 4' - dimethyl bibenzyl (**5**) and 3-methyl-6-[2(4'-methyl-4'-hydroxy)cyclohexane-2-one]-ethyl cyclohexa-2-en-1-one (**6, 41%**)[16]. The structure elucidation of compound **3** proved challenging due to the absence of analogous system in the literature.

The spiroketal **3**, $C_{16}H_{24}O_4$ (MS, M^+280) has one carbonyl group [IR, 1710 cm^{-1}, UV(MeOH) λ_{max} 272 nm (ε_{max} 64.4) and ^{13}C NMR δ 209] and the remaining three oxygen atoms are present as ether linkage (^{13}C NMR singlets at δ 107, 96, 87 and 85). The ^1H & DEPT NMR spectra revealed the presence of three tertiary methyl (δ 1.40, 1.35, 1.30, s) , acetyl (δ 2.1, s) and six methylene groups (δ 1.3-2.8, m). The ^{13}C-^1H NMR, ^1H-^1H chemical shift correlation and ROESY experiments provided definitive assignments for all protonated carbons. Additional five quaternary carbons singlets discernable in the ^{13}C NMRspectrum were assigned to four carbons with ether linkage at C_4, C_6, C_8 & C_{11} and one quarternary carbon at C_1.

The possible mechanisam to formatiom of **3** is, **a**. acid catalysed carbonyl attack by enol ether, **b**. nucleophilic addition of carbonyl oxygen to the resulting to the cation, **c**. interception of the oxacarbenium from step **b** to form the acetal. This unique cyclization may be due to the stabilization of intermediate carbocation by ZSM-5.[17]

The complete structure of **3** was established by X-ray crystal structure analysis.[18] An ORTEP diagramme of **3** is provided in Figure 1 which has revealed the unique structural features: the ring 1 [C(1), C(2), C(3), C(4), C(11)] is in envelope conformation, ring 2 [C(1), C(11), C(4), O(5), O(6)] is in half chair conformation, ring 3 [C(1), C(11), O(12), C(8), O(7), C(6)], ring 4 [C(1), C(2), C(3), C(4), O(5), C(6)] and ring 6 [C(1), C(10), C(9), C(8), O(12), C(11)] are in the boat conformation and the ring 5 [C(1), C(10), C(9), C(8), O(7), C(6)] is in twisted boat conformation.

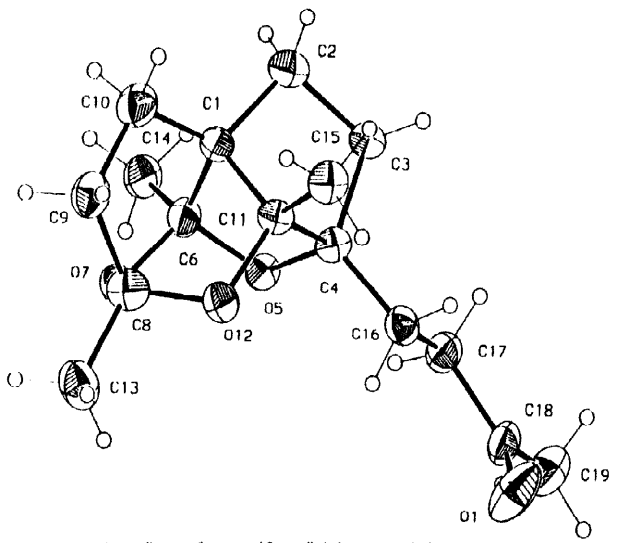


Figure 1 ORTEP diagram of compound 3, small circles represent hydrogen atoms.

In summary, we have achieved convenient synthesis of novel trioxatetracyclo[5.3.2.0.^{4,9}.0 ^{4,11}]-dodecane skeleton through the cyclization of diketo-olefin system over H-ZSM-5. Thus complex system is obtained from simple starting material, demonstrating the new use of H-ZSM-5 and present report also provides convinient route to bibenzylic skeletons.

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14. Compound **2**, I.R (Neat): 1712, 1431, 1368 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 2.1 (6H, s, 2 CH_3), 2.08 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.5-2.5 (12H, m $6CH_2$).^{13}C NMR, ($CDCl_3$): δ 202, 201, 196, 145, 101, 84, 42, 37, 30, 29.5, 29, 27, 26, 25, 21, 16. *mass*: $^m/_z$ 280 (M^+).

15. Compound **3**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.8 (1H, ddd, J=5.86, 9.88 and 15.56 Hz), 2.5 (1H, ddd, J=5.83, 9.33 and 15.19 Hz), 2.0 (1H, ddd, J=5.85 and 15.19 Hz), 1.7 (1H, ddd, J=5.85. 9.52 and 15.38 Hz), 2.1(3H, s,-CO$\underline{CH_3}$),1.40 (3H,s),1.35(3H, s),1.30 (3H, s),1.3-1.7 (8H, m).^{1}NMR (125 MHz, $CDCl_3$): δ 209,108,96,87,85,46,38,32,31,30,25,24,23,19,18,16. *mass*: $^m/_z$ 280 (M^+).

16. Compound**4**:I.R(Nujol):3350,1650cm^{-1}.^{1}HNMR(300MHz,$CDCl_3$):δ8.08(OH,s,D_2Oexchangeable), 6.92 (1H, d, J=7.5 Hz), 6.75 (1H, s), 6.3 (1H, d, J=7.5 Hz), 5.92 (1H, s), 2.27 (3H, s), 2.6-1.6 (9H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204 (s), 164 (s), 155 (s), 137 (s), 130 (d), 126 (d), 124 (s), 120 (d), 117 (d), 44 (d), 31, 30, 28, 27, 24, 21 (4t, 2q). *mass*: $^m/_z$ 244.(M^+).Compounds **5&6** could not be separated, characterized through GC-MS and spectral properties of the mixture.

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18. Crystal data for **3**: $C_{16}H_{24}O_4$, M = 280.35, monoclinic space group $P2_1$ with cell dimentions a = 8.727 (1) Å, b = 9.162 (4) Å, c = 10.205 (2) Å. V = 761.6 (4) $Å^3$, Z = 2, d_{calcd} = 1.223 M gm^{-3}, Absorption coefficient = 0.701 mm^{-1}, F (000) = 304. Crystal size of 0.27 x 0.32 x 0.45 mm was mounted on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite-monochromated CuK α X-ray source (λ = 1.5418 Å). The unit cell parameters were obtained using the method of short vectors followed by least-squares refinement of 25 reflections. All 25 reflections could be indexed with respect to a monoclinic unit. Lorentz and polarization corrections were applied. The crystal structure was solved by SHELXS-86.[19] The anisotropic full-matrix refinement of the nonhydrogen atoms and isotropic refinement of the hydrogen atoms fixed in calculated positons using SHELXL-93[20] [1240 unique reflections with $I > 2\sigma(I)$]. 181 parameters have been refined using 1240 unique reflections to R = 0.0575, wR2 = 0.1754. In the final difference map$(\Delta\sigma)_{max}$ = 0.001 and $(\Delta\rho)_{min}$ =- 0.200, $(\Delta\rho)_{max}$ = 0.409 $eÅ^{-3}$. All calculations were performed on MicroVax 3100 computer.

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