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CYCLOBUTYL-CYCLOPROPYLCARBINYL TYPE REARRANGEMENT OF 1-OXASPIROHEXANE DERIVATIVES. A NEW ENTRY TO FUNCTIONALIZED NORCARANES

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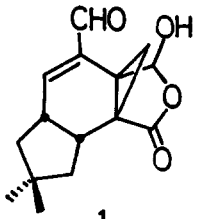
Summary: The acid-catalyzed rearrangement of the 1-oxaspirohexane derivatives 2a,b,d gave the corresponding functionalized norcaranes 3a,b,d in moderate to good yields.

Considerable interest has been shown on the marasmane sesquiterpenes[1] such as marasmic acid (1)[2] because of their novel structure and interesting biological activities. Central to the structural feature of the marasmanes is the norcarane skeleton with a variety of functionalities which would be formed by acid-catalyzed rearrangement of the 1-oxaspirohexane derivatives 2 incorporated into bicyclo[3.2.0] framework as shown below. In this connection, as part of our works on natural product synthesis via oxaspirohexane rearrangement,[3] we report herein the cyclobutyl-cyclopropylcarbinyl type rearrangement of 2 leading to the norcaranes 3 with functionalities useful for further elaboration to marasmanes.



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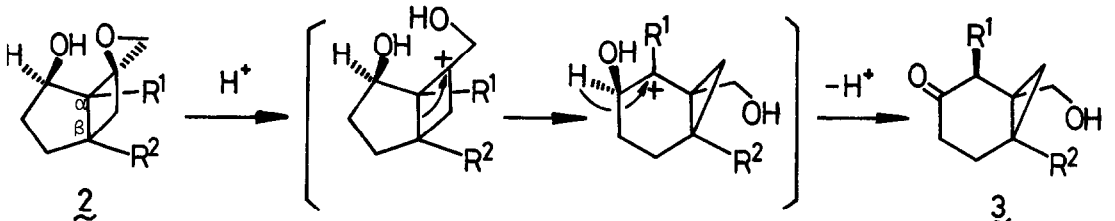
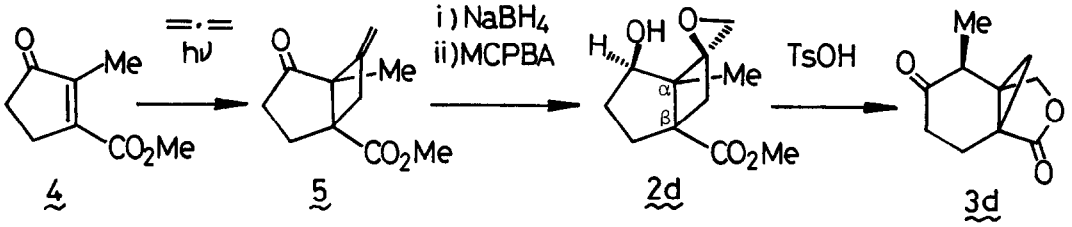


2 3

a R^1=Me, R^2=H; b R^1=R^2=Me; c R^1=H, R^2=Me

In order to test our hypothesis, the rearrangement of the oxaspirohexanes 2a-c[4] with different pattern of methyl substitution at the α and β positions, which were prepared regio- and stereoselectively from the corresponding enones,[5] was examined. Of a variety of conditions, (A) p-toluenesulfonic acid (TsOH), CH_2Cl_2, rt and (B) acid clay, CH_2Cl_2, rt were most satisfactory. In the case of 2a with an α methyl group, the desired norcarane 3a was obtained successfully as a sole product in (A) 92% or (B) 80% yield. Similarly, 2b with two methyl groups afforded 3b in (A) 30% or (B) 50% yield. On the other hand, reaction of 2c without α methyl substituent resulted in (A) formation of complex mixture of products or (B) no reaction. These results are reasonably interpreted by the substituent effect which stabilizes the cyclopropylcarbinyl type cation intermediate.



With the above results, we next examined the rearrangement of 2d with an ester group at the β position as a model study for the synthesis of marasmic acid (1). Photocycloaddition of the enone 4[6] to allene gave the Head to Head adduct 5[7] in 50% yield. Reduction of 5 with sodium borohydride followed by MCPBA oxidation afforded 2d in 67% overall yield. While 2d was innert to acid clay, the desired rearrangement took place smoothly with TsOH to furnish the lactone 3d derived from the concomitant lactonization in 70% yield. Application of the above rearrangement to the synthesis of marasmane sesquiterpenes is now being undertaken in our laboratories.

References and Notes

1. O. Sterner, R. Bergman, J. Kihlberg, and B. Wickberg, J. Nat. Prod., 48, 279 (1985) and references cited therein.
2. J.J. Dugan, P. de Mayo, M.N. Nisbet, J.R. Robinson, and M. Anchel, J. Am. Chem. Soc., 88, 2838 (1966). For total syntheses; W.J. Greenlee and R.B. Woodward, ibid., 98, 6075 (1976); Tetrahedron, 36, 3367 (1980); R.K. Boeckman, Jr. and S.S. Ko, J. Am. Chem. Soc., 102, 7149 (1980).
3. (a) Y. Tobe, S. Yamashita, T. Yamashita, K. Kakiuchi, and Y. Odaira, J. Chem. Soc., Chem. Commun., 1984, 1259; (b) Y. Tobe, T. Yamashita, K. Kakiuchi, and Y. Odaira, ibid., 1985, 898; (c) Y. Tobe, T. Kishida, T. Yamashita, K. Kakiuchi, and Y. Odaira, Chem. Lett., 1985, 1437.
4. All new compounds gave satisfactory analytical and spectral data. Selected data for 3a,b,d are as follows: 3a; IR 3350, 1700 cm^{-1}; ^1H NMR (CCl_4) δ 3.85(d, J=11 Hz, 1H), 3.23(s, 1H), 2.86(d, J=11 Hz, 1H), 2.82(q, J=7 Hz, 1H), 1.1-2.6 (m, 5H), 1.09(d, J=7 Hz, 3H), 0.2-0.6 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 214.9(s), 68.6(t), 42.2(d), 35.5(t), 28.9(s), 22.5(t), 17.0(d), 12.2(q), 10.3(t). 3b; IR 3400, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97(d, J=12 Hz, 1H), 3.37 (d, J=12 Hz, 1H), 2.91(q, J=7 Hz, 1H), 1.4-2.6 (m, 5H), 1.34(s, 3H), 1.19(d, J=7 Hz, 3H), 0.56(d, J=6 Hz, 1H), 0.24(d, J=6 Hz, 1H). 3d; mp 96-97.5 °C; IR 1750, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (AB, J=9 Hz, 2H), 2.0-2.9 (m, 5H), 1.18(d, J=7 Hz, 3H), 1.15(AB, J=6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 209.9(s), 176.8(s), 72.6(t), 44.2(d), 35.7(s), 35.1(t), 25.7(s), 21.8(t), 20.3(t), 13.1(q).
5. The epoxides 2b and 2c were prepared from 1,2-dimethyl- and 1-methylcyclopenten-3-ones, respectively, by i) photocycloaddition to allene, ii) lithium aluminum hydride reduction, and iii) m-chloroperbenzoic acid (MCPBA) oxidation in similar yields and selectivities to those of 2a reported previously.[3c]
6. Prepared by oxidation (CrO_3, pyridine) of methy 2-methylcyclopentene-1-carboxylate: K.E. Harding, K.S. Clement, J.C. Gilbert, and B. Wiechman, J. Org. Chem., 49, 2049 (1984).
7. The H-H/H-T orientation of 5 was confirmed by conversion of 5 into the Head to Head adduct of 1,2-dimethylcyclopenten-3-one with allene.[5]

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