Pergamon

Tetrahedron Letters, Vol. 35, No. 50, pp. 9329-9332, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02074-4

THE STRUCTURE of β-ISOPIPITZOL

Francisco Yuste,* Héctor Barrios, Eduardo Díaz, Benjamín Ortiz, Rubén Sánchez-Obregón and Fernando Walls

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México D. F.

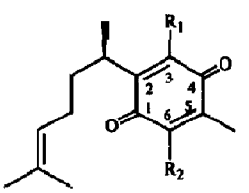
Abstract: The Lewis acid catalyzed intramolecular cycloaddition of isoperezone (**5**) produced a tricyclic compound containing a new skeleton named β-isopipitzol (**6**), perezinone (**7**) and dihydroisoperezinone (**8**).

The thermal conversion of sesquiterpene quinone perezone (**1**)[1] into an equimolecular mixture of the cedranoids α-pipitzol (**2**) and β-pipitzol (**3**)[2] is a spectacular example[3] of a concerted [π4s + π2s] cycloaddition of a pentadienyl cation to an olefin.[4] However, in the thermal transformation there is a lack of asymmetric induction by the chiral center of **1** that has been attributed to the fact that relative high temperatures are required to activate the reaction. Then, it was found that a mild highly stereoselective cycloaddition, favoring the α-isomer **2** in a 9:1 ratio, could be carried out by $BF_3{\cdot}Et_2O$ catalyzed treatment of **1** at low temperature.[5] In this case, however, the conversion follows a stepwise mechanism. Later studies revealed that the stereoselectivity of **1** to **2** + **3** transformation could be changed, up to 1:8 in favor of the β-isomer **3**, when O-methylperezone (**4**) is treated with Lewis acids such as $AlCl_3/Et_2S$[6] or $BF_3{\cdot}Et_2O$,[7] presumably due to steric crowding between the secondary methyl and the methoxyl groups in the transition state.

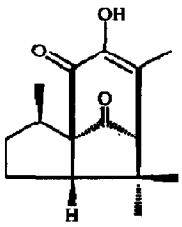
Recently,[8] we have reported the isomerization of perezone (**1**) into isoperezone (**5**) by means of a 1,2-carbonyl transposition catalyzed by 3,4,5,6-tetrahydro-2-pyrimidinethiol. The $BF_3{\cdot}Et_2O$ treatment of **5** produced dihydroisoperezinone (**8**).[8] In this paper, we want to report the structure and stereochemistry of the product obtained by $ZnBr_2$ catalyzed intramolecular cycloaddition of **5**, which we named β-isopipitzol (**6**).

When isoperezone (**5**) is heated at its melting point for 0.5 h or refluxed in toluene or xylene solution for several hours, it remains practically unchanged. However, the reaction of **5** with 2 eq. of $ZnBr_2$ in CH_2Cl_2 solution at room temperature for 72 h produced essentially three products (**6-8**) which were separated and purified by flash chromatography. Compounds **7** (perezinone)[2, 9] and **8** (dihydroisoperezinone)[8] were obtained in 29% and 2% yield, respectively, and were identified by spectroscopic and TLC comparison with authentic samples. The tricyclic compound **6** was obtained as colorless crystals in 20% yield. The use of Eu $(fod)_3$ as catalyst affords a mixture of **6** (13%) and **8** (51%), whereas the treatment of **5** with $BF_3{\cdot}Et_2O$ leads to **8** as only product in 32% yield.[8]

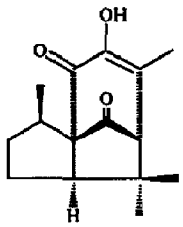
The structure and stereochemistry of β-isopipitzol (**6**)[10] containing a new skeleton was established by spectroscopic methods, mainly 2D ^1H- and ^{13}C-NMR, and confirmed by a single crystal X-ray diffraction study. Product **6** gives positive ferric chloride test and exhibits UV absorptions at 244 (sh) and 284 nm (log ε 3.36, 3.95). The IR spectrum ($CHCl_3$) presents bands at 3464 (OH), 1756 (cyclopentanone) and 1676 and 1632 cm-1 (six-membered enolized α-diketone). The EIMS shows a molecular ion at m/z 248 and the base peak at m/z 167.



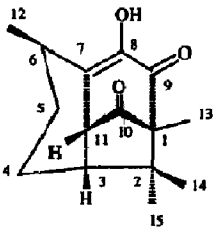
1 R_1=OH; R_2=H
4 R_1=OMe; R_2=H
5 R_1=H; R_2=OH



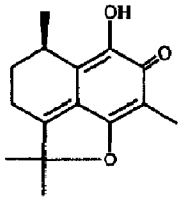
2



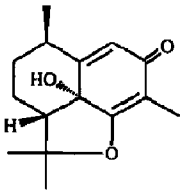
3



6



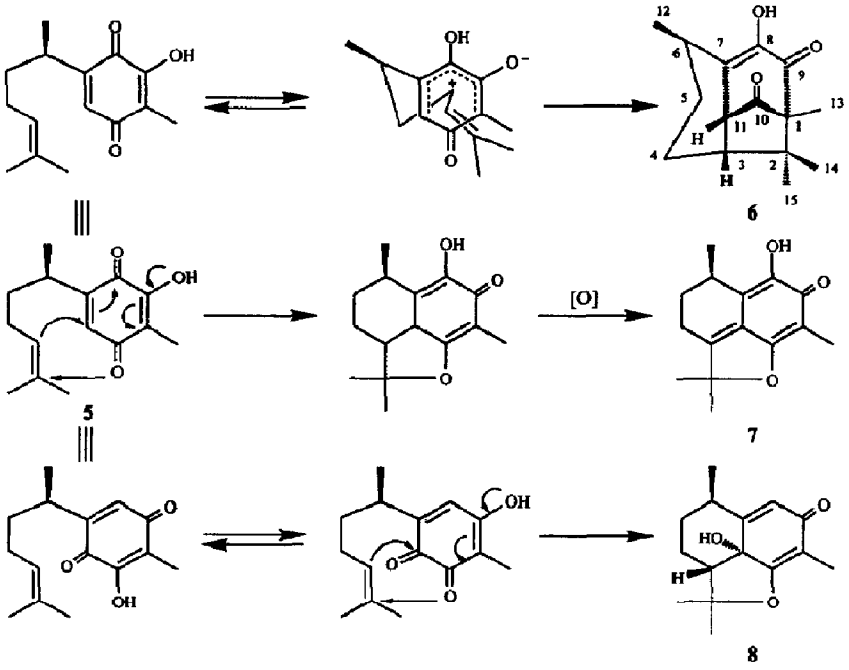
7



8

The ^{1}H-NMR ($CDCl_3$) spectrum showed three methyl singlets and a methyl doublet, one proton broadened singlet at δ 5.98 which disappears with D_2O, a single proton multiplet at δ 3.17 (H-6), one proton doublet at δ 3.12 (J= 7.2 Hz, H-11), a single proton doublet of doublet of doublet at δ 2.43 (J= 9.0, 9.0, 7.2, H-3) and four additional multiplets which integrated one proton each. The ^{13}C-NMR ($CDCl_3$) spectrum showed four non-protonated carbons between δ 140 and δ 207 and eleven saturated carbons (four CH_3, two CH_2, three CH and two quaternary carbons). The NMR assignments[10] were made by 2D COSY, COLOC and HETCOR experiments.[11] Evidences about the stereochemistry of **6** were supported by NOEDS[11] recorded on ^{1}H-NMR (C_6D_6). Irradiation of the Me-12 at δ 0.93 showed NOE effects at the vicinal H-6 (δ 3.20), H-11 (δ 2.90) and H-5eq (δ 1.45). When the H-3 signal at δ 1.89 was irradiated, NOE is seen at H-11 and Me-14 group (δ 0.64) and irradiation on H-11 proton showed NOE enhancements for H-3 and Me-12 signals. These results are evidence that Me-12, H-11 and H-3 are all in a *cis* relationship.

The conversion of **5** to **6-8** can be rationalized *via* the intermediates depicted in Scheme 1. The formation of α- and β-pipitzols (**2** and **3**) through *exo* transition states is in accord with the well known high preference for *exo* adducts in intramolecular Diels-Alder cycloadditions when a three-atom *ansa* is involved.[12] In the case of β-isopipitzol (**6**), an examination of molecular models suggests that the *endo* transition state is less strained than the *exo* transition state. A *trans*-fused cycloadduct (*exo*) would appear to be highly strained and thus its formation rather unlikely. In addition, the H-3, H-11 coupling constant of 7.2 Hz observed in the 300 MHz ^{1}H-NMR spectrum of **6** is clearly consistent with a dihedral angle of 33.2° (calculated by using the MM2 molecular mechanics program[13]) for the *endo* adduct. A single crystal X-ray structural study confirmed the stereochemistry of β-isopipitzol (**6**). Figure 1, shows a computer-generated perspective drawing of **6**. As can be seen, the cyclohexane and cyclopentanone rings are *cis*-fused and H-3, H-11 are *cis* to the secondary methyl group. The complete π-facial diastereoselectivity observed in the Lewis acid catalyzed cyclization of **6** (no trace of the diastereoisomeric *endo* adduct was obtained) is attributed to the preferential formation of the *endo* transition state shown. This transition



Scheme 1

state is favored over the alternative, double bond attack from the opposite side of the ring, because of steric interaction between the secondary methyl substituent and the chelated complex formed by coordination of the Lewis acid with the bidentate substrate **5**. The transformation of isoperezone (**5**) into perezinone (**7**) could be derived from an electrophilic attack on the side chain double bond by the Lewis acid polarized p-quinone system, followed by cyclization and air oxidation of the dihydroperezinone intermediate.[2, 9] A similar intramolecular electrophilic attack on the side chain double bond by a Lewis acid polarized o-quinone system and cyclization has been proposed[8] for the conversion of isoperezone (**5**) into dihydroisoperezinone (**8**).

Finally, it is noteworthy that the transformation of isoperezone (**5**) into β-isopipitzol (**6**) constitutes a rare example[14] of a [4+2] intramolecular cycloaddition through a 2-substituted cyclopentadienyl cation.

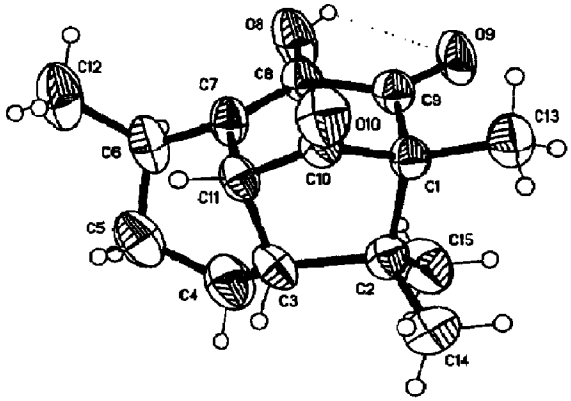


Figure 1. ORTEP plot of **6**

Acknowledgments: We thank R. Patiño, M. I. Chávez, R. Gaviño, J. Pérez, L. Velasco and S. Hernández for their technical assistance.

REFERENCES AND NOTES

1. For a review on this molecule, see: Joseph-Nathan, P.; Santillan, R. L., *Studies in Natural Product Chemistry*, vol. 5 Structural Elucidation (Part B), ed. Atta-ur-Rahman; Elsevier Science Publishers: Amsterdam. 1989; pp. 763-813.
2. Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Escobar, M.; Romo, J., *Tetrahedron*, **1966**, 22, 2387-2399.
3. Carruthers, W., *Cycloaddition Reactions in Organic Synthesis*, (Tetrahedron Organic Chemistry Series; vol. 8); Pergamon Press: Oxford. 1990; pp. 209-240.
4. Joseph-Nathan, P.; Mendoza, V.; García, E., *Tetrahedron*, **1977**, 33, 1573-1576.
5. Sánchez, I. H.; Yañez, R.; Enríquez, R.; Joseph-Nathan, P., *J. Org. Chem.*, **1981**, 46, 2818-2819.
6. Sánchez, I. H.; Basurto, F.; Joseph-Nathan, P., *J. Nat. Prod.*, **1984**, 47, 382-383.
7. Joseph-Nathan, P.; Burgueño-Tapia, E.; Santillan, R. L., *J. Nat. Prod.*, **1993**, 56, 1758-1765.
8. Rodríguez-Hernández, A.; Barrios, H.; Collera, O.; Enríquez, R. G.; Ortiz, B.; Sánchez-Obregón, R.; Walls, F.; Yuste, F.; Reynolds, W. F.; Yu, M., *Nat. Prod. Lett.*, **1994**, 4, 133-139.
9. Archer, D. A.; Thomson, R. H., *J. Chem. Soc. (C)*, **1967**, 1710-1716.
10. Compound **6**: mp 146-8°C (acetone-hexane); $[\alpha]_D$ -186.4° (c= 0.5, $CHCl_3$); UV (MeOH): λ_{max} 244 (sh), 284 (log ε 3.36, 3.95); IR ($CHCl_3$): ν_{max} 3464, 1756, 1676, 1632 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 (s, 3H, Me-15), 0.96 (s, 3H, Me-14), 1.10 (m, J= 13.8, 13.0, 9.0, 2.7 Hz, 1H, H-4ax), 1.17 (s, 3H, Me-13), 1.18 (d, J= 6.9 Hz, 3H, Me-12), 1.30 (m, J= 13.2, 13.0, 9.0, 3.0 Hz, 1H, H-5ax), 1.60 (m, J= 13.8, 9.0, 3.0, 3.0 Hz, 1H, H-4eq), 1.92 (m, J= 13.2, 6.9, 3.0, 2.7 Hz, 1H, H-5eq), 2.43 (ddd, J= 9.0, 9.0, 7.2 Hz, 1H, H-3), 3.12 (d, J= 7.2 Hz, 1H, H-11), 3.17 (m, J=9.0, 6.9, 6.9 Hz, 1H, H-6), 5.98 (s, 1H, interchangeable with D_2O, enolic OH); ^{1}H-NMR (200 MHz, C_6D_6): δ 0.63 (s, 3H, Me-15), 0.64 (s, 3H, Me-14), 0.77 (m, 1H, H-4ax), 0.82 (m, 1H, H-5ax), 0.93 (d, J= 6.8 Hz, 3H, Me-12), 1.05 (m, 1H, H-4eq), 1.30 (s, 3H, Me-13), 1.45 (m, 1H, H-5eq), 1.89 (m, 1H, H-3), 2.90 (d, J=6.8 Hz, 1H, H-11), 3.20 (m, 1H, H-6), 7.88 (s, 1H, interchangeable with D_2O, enolic OH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 8.0 (C-13), 16.6 (C-12), 21.0 (C-4), 21.6 (C-15), 29.1 (C-14), 32.2 (C-6), 32.4 (C-5), 44.9 (C-2), 46.8 (C-11), 47.9 (C-3), 70.5 (C-1), 140.7 (C-7), 143.6 (C-8), 195.1 (C-9), 206.6 (C-10); EIMS m/z (rel. int.): 248 (M^+, 61), 233 (13), 205 (22), 177 (15), 167 (100), 166 (38), 153 (24), 149 (21), 138 (28), 136 (20), 89 (23), 77 (42), 69 (27). Crystal data: $C_{15}H_{20}O_3$, M_w = 248.3, colorless crystals, 0.38x0.36x0.10 mm, orthorhombic, $P2_12_12_1$ with a = 6.757 (3), b = 12.407 (4), c = 16.263 (6) Å with D_c = 1.210 g cm^{-3} for Z = 4, V= 1363.3 (7) $Å^3$, T = 298 K, λ (CuKα) = 1.54178 Å, μ= 0.667 mm^{-1}, F (000) = 536 R = 0.0583, R_W = 0.0749 for 792 observed reflections.
11. Nakanishi, K., *One-dimensional and Two-dimensional NMR Spectra by Modern Pulse Techniques*; University Science Books: Mill Valley, California. 1990; pp. 66-186.
12. Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P., *Natural Product Synthesis Through Pericyclic Reactions*, (ACS Monograph; 180), American Chemical Society: Washington, D.C. 1983, pp. 164-203.
13. Allinger, N. L., *J. Am. Chem. Soc.*, **1977**, 99, 8127-8134.
14. For a similar reaction, see: Hienuki, Y.; Tsuji, T.; Nishida, S., *Tetrahedron Lett.*, **1981**, 22, 867-870.

(*Received in USA* 15 *September* 1994; *revised* 12 *October* 1994; *accepted* 14 *October* 1994)