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An Efficient Synthesis of 9-Oxaisotwist-8-en-2-ones. Synthesis of Deoxysilydianin Methyl Ether

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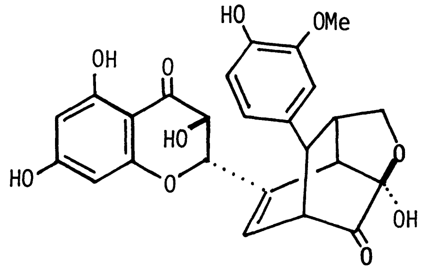
Deoxysilydianin methyl ether has been readily synthesized by means of anodic oxidation of the corresponding phenol as a key step, indicating a general method for synthesis of 9-oxaisotwist-8-en-2-ones in high yields.

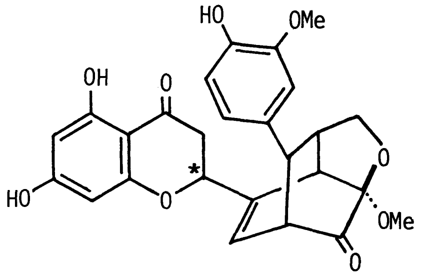
In connection with our structural and synthetic studies1) on bioactive natural products with a bicyclo[2.2.2]octane ring system, silydianin (1) as an antihepatotoxic agent,2) which has been isolated from the fruits of Silybum marianum G., is quite interesting from view points of both molecular structure and physiological activity. In the present paper, we wish to describe a facile synthesis of deoxysilydianin methyl ether (2a) and its diastereoisomer (2b), both of which have the same 9-oxaisotwist-8-en-2-one ring system as that of silydianin (1), using electrochemical method.

When treated with 2-(trimethylsilyl)ethoxymethyl chloride (1.05 equiv.) in CH_2Cl_2 containing Pr^i_2NEt (1.25 equiv.) (room temp, 3.7 h, under argon), 3,4-dihydroxybenzaldehyde was selectively converted into a desired ether (3)3) in 85% yield. This ether (3) was further treated with an allyl alcohol (4) (1.5 equiv.) in THF containing Ph_3P (1.5 equiv.) and diethyl azodicarboxylate (1.5 equiv.) (room temp, 24 h, under argon)4) to afford the corresponding allyl ether (5),3) in 55% yield, which was then deprotected with $Bu^n_4N^+F^-$ (4 equiv.) in THF (45 °C, 30 h, under argon) to give rise to a desired phenol (6)3) in 82% yield.

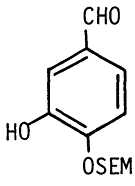
On the other hand, 3-acetoxy-4-hydroxybenzaldehyde, which was produced by acetylation of 3.4-dihydroxybenzaldehyde [AcCl (1.1 equiv.)/NaH (1.1 equiv.) in DMF (-55 °C - room temp, 5 h], was readily converted into another phenol (7)3) in 2 steps [1) 8/Ph_3P (1.2 equiv.)/EtOOCN=NCOOEt (1.2 equiv.) in THF (room temp, 22 h, under argon) (30% yield); 2) K_2CO_3 (1.1 equiv.) in MeOH (room temp, 30 min, under argon) (84% yield)]. This phenol (7) was oxidized with $Tl(NO_3)_3$ (TTN) (1.5 equiv.) in MeOH (-26 - -20 °C, 3.7 h, under argon)5) to afford two 9-oxaisotwist-8-en-2-ones (9 and 10)3) in 43 and 36% yields, respectively. The latter (10) was quantitatively converted into the corresponding aldehyde (9) on treatment with 2M HCl in acetone (room temp, 40 min), indicating that the total yield of 9 was ca. 80% from 7. In the case of TTN oxidation of the phenol (6), however, any tricyclic compound has not been obtained. Probably, one of some reasons is that



1



2a,b



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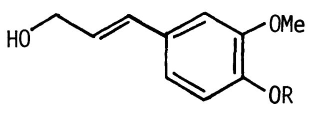
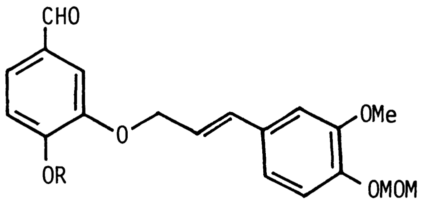


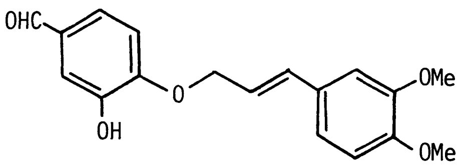
4 R = CH_2OMe

8 R = Me



5 R = $CH_2OCH_2CH_2SiMe_3$

6 R = H



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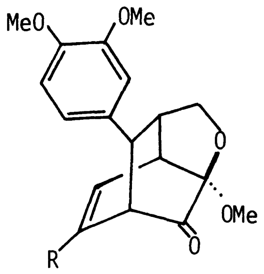
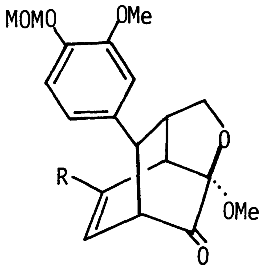


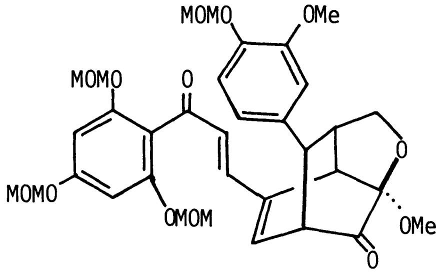
9 R = CHO

10 R = $CH(OMe)_2$



11 R = CHO

12 R = $CH(OMe)_2$



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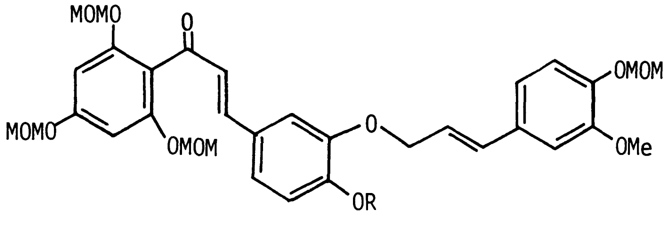

13 R = $CH_2OCH_2CH_2SiMe_3$

14 R = H

6 has a methoxymethyl ether group labile to acid. Recently, a general synthesis of isotwist-8-en-2-ones from *o*-(3-butenyl)phenols using $Pb(OAc)_4$ - AcOH has been reported by Yates *et al.*6) However, their yields are low (20 - 30%). In addition, this Wessely oxidation, which is carried out under acidic conditions, can not be used for such an acid-sensitive phenol as 6. Fortunately, we could synthesize two 9-oxaisotwist-8-en-2-ones (11 and 12) by means of electrochemical method, as follows.

When electrolyzed at a constant current [3.3 mA (+860 - 1100 mV *vs*. SCE; *ca*. 2 F/mol][7] in MeOH - THF (3 : 2) using $LiClO_4$ as a supporting electrolyte, the phenol (**6**) was successfully converted into the tricyclic compounds (**11** and **12**)[3] in 12 and 79% yields, respectively.[8]

Thus, the aldehyde (**5**) was reacted with 2,4,6-trihydroxyacetophenone methoxymethyl ether in benzene containing Triton B (4 equiv.) (room temp, 24 h, under argon) to afford a condensation product (**13**),[3] in 84% yield, which was further treated with $Bu^n_4N^+F^-$ in THF (45 °C, 20 h, under argon) to give rise to a desired phenol (**14**)[3] in 87% yield. On electrolysis at a controlled potential (+950 mV *vs*. SCE; *ca*. 2 F/mol) in MeOH - THF (2 : 1) using $LiClO_4$ as a supporting electrolyte,[7] the phenol (**14**) was also converted into a 9-oxaisotwist-8-en-2-one (**15**),[3] in 82% yield, which was subjected to deacetalization with conc.HCl in MeOH (refluxing temp, 5 min) followed by cyclization using NaOAc (50 equiv.) in EtOH (70 °C, 2 h) to afford deoxysilydianin methyl ether (**2a**) and its diastereoisomer (**2b**) in 71% overall yields (relative ratio: **2a**/**2b** = *ca*. 1).[9] Further synthetic study on silydianin (**1**) and related compounds are in progress using the 9-oxaisotwist-8-en-2-ones (**2a** and **15**).

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References

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3) The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: **3** as an oil: $C_{13}H_{20}O_4Si$ [m/z 268.1100(M^+)]; IR (film) 3400, 1670, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.95(2H, t, J= 9 Hz), 3.77(2H, t, J= 9 Hz), 5.31(2H, s), 6.25(1H, br.s, OH), 7.1 - 7.5 (3H, aromatic), and 9.83(1H, s). **5** as an oil: $C_{25}H_{34}O_7Si$ [m/z 474.2090(M^+)]; IR (film) 1690, 1590, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.94(2H, t, J= 9 Hz), 3.50(3H, s), 3.80(2H, t, J= 9 Hz), 3.87(3H, s), 4.78(2H, d, J= 6 Hz), 5.20(2H, s), 5.34(2H, s), 6.26(1H, dt, J= 16, 6 Hz), 6.8 - 7.5(6H, aromatic), 6.68(1H, d, J= 16 Hz), and 9.86(1H, s). **6**: mp 124 - 125 °C; $C_{19}H_{20}O_6$ [m/z 344.1283 (M^+)]; IR (Nujol) 3350 (br), 1660, 1580, and 1500 cm^{-1}. **7**: mp 135 - 137 °C; IR (Nujol) 3400, 1670, 1600, 1580, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.91(3H, s), 3.93(3H, s), 4.80(2H, d, J= 6 Hz), 5.93(1H, br.s, OH), 6.23(1H, dt, J= 15, 6 Hz), 6.68(1H, d, J= 15 Hz), 6.8 - 7.5(6H, complex), and 9.83(1H, s). **9**: mp 179 - 182 °C; $C_{19}H_{20}O_6$ [m/z 344.1276(M^+)]; IR (Nujol) 1735, 1670, 1615, 1605, 1580, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.90(1H, m), 3.44(1H, m), 3.63(3H, s), 3.65 - 4.00(2H, complex), 3.86(3H, s), 3.87(3H, s), 4.01(1H, d, J= 8 Hz), 4.33

(1H, dd, J= 3, 8 Hz), 6.47(1H, dd, J= 2, 9 Hz), 6.57(1H, d, J= 2 Hz), 6.72(1H, d, J= 9 Hz), 7.2 - 7.3(1H, m), and 9.43(1H, s). 10 as an oil: $C_{21}H_{26}O_7$ [m/z 362.1728(M^+- CO)]; IR (Nujol) 1730, 1640, 1600, 1590, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$) = 2.94(3H, s) and 3.22(3H, s). 11: mp 105 - 106 °C; $C_{20}H_{22}O_7$ [m/z 374.1360(M^+)]; IR (Nujol) 1750, 1680, 1615, 1605, 1590, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.81(1H, m), 3.43(1H, m), 3.47(3H, s), 3.49(3H, s), 3.60(1H, dd, J= 3, 7 Hz), 3.80(3H, s), 3.94(1H, d, J= 8 Hz), 4.16(1H, dd, J= 2, 5 Hz), 4.28 (1H, dd, J= 4, 8 Hz), 5.14(2H, s), 6.43(1H, dd, J= 2, 9 Hz), 6.55(1H, d, J= 2 Hz), 6.97(1H, dd, J= 2, 7 Hz), 7.01(1H, d, J= 9 Hz), and 9.65(1H, s). 12 as an oil: $C_{22}H_{28}O_8$ [m/z 420.1778(M^+)]; IR (film) 1745, 1585, and 1515 cm^{-1}; ^1H NMR δ = 3.30(3H, s) and 3.43(3H, s). 13 as an oil: IR (film) 1640, 1600, and 1510 cm^{-1}; ^1H NMR δ = 0.95(2H, t, J= 8 Hz), 3.37(6H, s), 3.50(6H, s), 3.78(2H, t, J= 8 Hz), 3.87(3H, s), 4.74(2H, d, J= 6 Hz), 5.07(4H, s), 5.14(2H, s), 5.18 (2H, s), 5.28(2H, s), 6.27(1H, dt, J= 16, 6 Hz), and 6.5 - 7.5(10H, complex). 14 as an oil: $C_{33}H_{38}O_{12}$ [m/z 626.2361(M^+)]; IR (film) 3400, 1630, 1600, 1580, and 1510 cm^{-1}. 15 as an oil: $C_{34}H_{40}O_{13}$ [m/z 656.2446(M^+)]; IR (film) 1740, 1645, 1600, 1590 (sh), and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.82(1H, m), 3.40(6H, s), 3.42 - 3.47(2H, complex), 3.48(3H, s), 3.49(3H, s), 3.55(3H, s), 3.81(3H, s), 3.82 - 3.83(1H, complex), 4.00(1H, d, J= 8.5 Hz), 4.31(1H, dt, J= 3.5, 8.5 Hz), 5.0 - 5.25(8H, complex), 6.28(1H, d, J= 5 Hz), 6.42(1H, dd, J= 2, 8.5 Hz), 6.53 - 6.55(3H, complex), 6.68(1H, d, J= 16 Hz), 6.98(1H, d, J= 8.5 Hz), and 7.12(1H, d, J= 16 Hz).

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7) A glassy carbon beaker and a platinum wire tip were used as an anode and cathode, respectively.

8) Although base-catalyzed reaction between 11 and 2,4,6-trihydroxyacetophenone methoxymethyl ether has been carried out under various conditions, any condensation product has not been obtained.

9) These two diastereoisomers have been easily separated by preparative TLC, and their spectral data may be assigned to 2a and 2b, respectively: 2a: mp 255 - 256 °C; $C_{26}H_{24}O_9$ [m/z 480.1450(M^+)]; IR (Nujol) 3300, 1730, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.75(1H, dd, J= 3, 17 Hz), 2.89(1H, m), 3.09(1H, dd, J= 12, 17 Hz), 3.22(1H, dd, J= 3, 7 Hz), 3.39(1H, m), 3.57(3H, s), 3.85(3H, s), 3.89(1H, dd, J = 2, 4 Hz), 3.97(1H, d, J= 8 Hz), 4.30(1H, dd, J= 3, 8 Hz), 5.31(1H, dd, J = 3, 12 Hz), 5.97(1H, d, J= 2 Hz), 6.01(1H, d, J= 2 Hz), 6.15(1H, d, J= 7 Hz), 6.68 (1H, dd, J= 2, 8 Hz), 6.75(1H, d, J= 8 Hz), and 6.85(1H, d, J= 2 Hz). 2b: mp 252 - 255 °C; $C_{26}H_{24}O_9$ [m/z 480.1446(M^+)]; IR (Nujol) 3350, 1730, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.81(1H, m), 2.87(1H, dd, J= 3, 17 Hz), 3.14(1H, dd, J= 11, 17 Hz), 3.23(1H, dd, J= 2, 7 Hz), 3.36(1H, m), 3.54(3H, s), 3.82(3H, s), 3.88(1H, dd, J= 3, 8 Hz), 3.95(1H, d, J= 8 Hz), 4.28(1H, dd, J= 3, 8 Hz), 5.29(1H, dd, J = 3, 11 Hz), 5.98(1H, d, J= 2 Hz), 6.04(1H, d, J= 2 Hz), 6.15(1H, d, J= 7 Hz), 6.46(1H, dd, J = 2, 8 Hz), 6.71(1H, d, J = 8 Hz), and 6.84(1H, d, J = 2 Hz).

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