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Serendipitous and acid catalyzed synthesis of spirolactones

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ABSTRACT

Formation of three diasteroisomeric spirodilactones **14a–c** and **11** has been reported from diester **13** and **9**, respectively, under the influence of mineral acid.

1. Introduction

Unique structure and reactivity pattern of spirocyclic compounds is of great interest to organic chemists. Spiro compounds possess homoconjugation (spiroconjugation) due to perpendicular π-electron systems and exhibit homoconjugation which is known as spiroconjugation.[1] Besides theoretical aspects spiro systems are also of industrial interest.[2] Spiro-lactone unit is present in several natural products, examples include: synringolide (**1**),[3] teusalvin (**2**),[4] secosyrin (**3**),[5] gaertneroside (**4**),[6] pathylactone (**5**),[7] and canangone (**6**)[8] (Fig. 1).

Various research group reported the synthesis of spirolactones using different reagents, such as manganese(III)acetate,[9] iron(III) perchlorate,[10] I_2,[11] Ag_2O treatment, followed by oxidation with $RuO_2/NaIO_4$ etc.

2. Result and discussions

In connection with our interest to prepare polycyclic compounds[12] we were interested in hydrolyzing the diester **9**, which was prepared from 1,3-cyclopentadiene (Cp) and dimethyl maleate (**7**) via Diels–Alder (DA) reaction[13] followed by alkylation with allyl bromide in presence of NaHMDS as a base. Under toluene reflux conditions bicyclic adduct **8**[14] was formed in 80% yield. Spectral evidence suggested that the formation of both *exo*- and *endo*-isomers. Allylation of compound **8** using NaHMDS gave only *trans*-isomer **9** as a sole product; irrespective of the stereochemistry of the starting DA adduct (*endo*- or *exo*-) (Scheme 1).

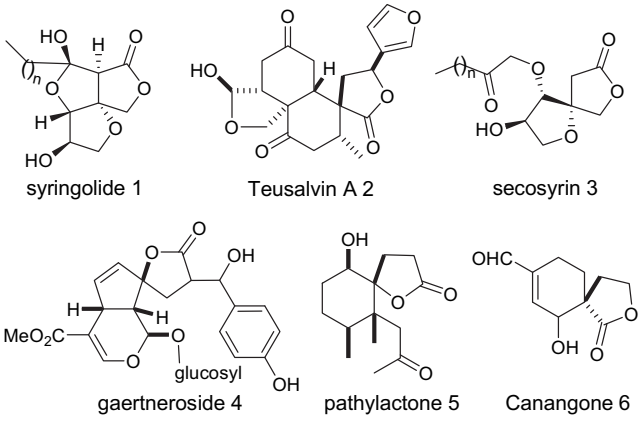
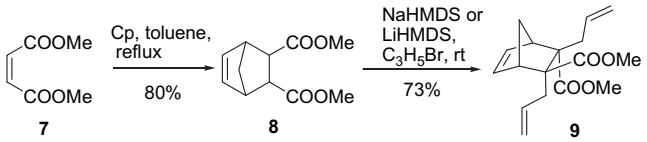


Fig. 1. Natural products containing spiro-lactone unit.



Scheme 1.

Here, the observed stereoselectivity can be explained on the basis of product like transition state where the two bulky ester groups are in *trans*-relation.[15a] Initially we choose alkaline hydrolysis condition[16] to hydrolyze the ester functionality of **9** to generate the diacid **10**. Unfortunately our efforts in this direction were not productive (Scheme 2).

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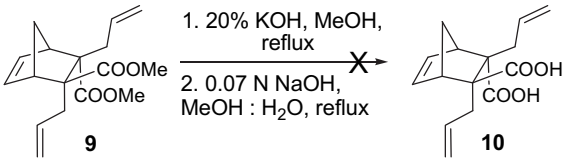
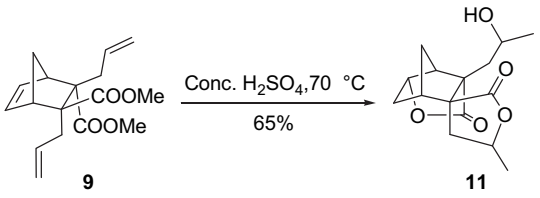


Scheme 2.

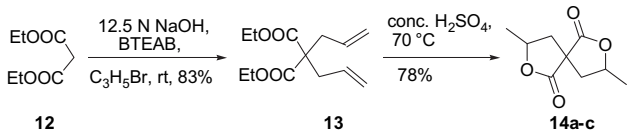
Later, our attention was directed toward the hydrolysis of the diester **9** under acidic conditions. As the ester moiety is attached to quaternary carbon, we first used formic and methansulfonic acid mixture for hydrolysis.[15b] Even after prolonged exposure there was no additional spot as indicated by TLC. Next, we attempted the hydrolysis with concd H_2SO_4 at 70 °C and the bis-lactone **11** was formed instead of the expected hydrolysis product. Under these reaction conditions hydration of residual double bond (which does not participated in lactone formation) was also observed (Scheme 3). Most probably the hydration may occur during the workup process. On the basis of ^1H and ^{13}C NMR spectral data the product formed was identified as **11**.



Scheme 3.

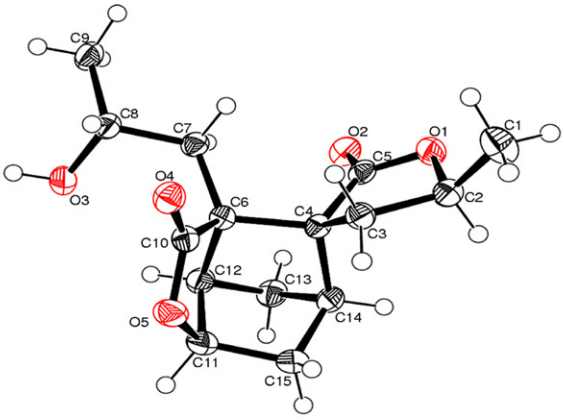
X-ray diffraction studies of the lactone **11** unambiguously proved its structure. Close inspection of product indicated that the distance between O–**H**···**O** is 2.023 Å and the angle is measured 162.68°, which suggests the moderately strong H-bonding between two molecules[17] (Fig. 2).

To test the scope of bis-lactone formation in presence of concd H_2SO_4, we have prepared diethyl diallylmalonate (**13**) by diallylation of diethyl malonate (**12**) under phase-transfer catalyst (PTC) conditions[18] in presence of 12.5 N NaOH. The resulting diallylated intermediate **13** on treatment with concd H_2SO_4 at 70 °C furnished a diastereomeric mixture of three bis-spirolactones **14a**–**c**. Three diastereomeric bis-spirolactones (**14a**–**c**) were separated through column chromatography in their racemic form as white crystalline solids in 2:1:1 ratio (Scheme 4). Structures of all the three diastereomers were determined with the aid of various spectral data, such as ^1H and ^{13}C spectroscopy and further supported by HRMS.



Scheme 4.

Molecular modeling suggests that among three possible structures one of them is unsymmetrical (**14a**). Due to lack of symmetry all the protons and carbons of this bis-lactones appeared distinctly different chemical shifts in ^1H and ^{13}C NMR spectral data. Other two diastereomers shows less number of proton and carbon peaks in their respective spectral data due to presence of symmetry elements.



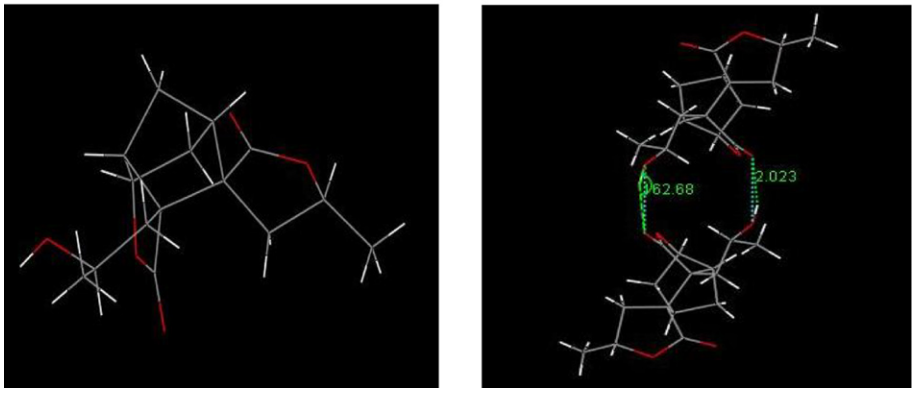


Fig. 2. Structure of **11** determined by X-ray diffraction which shows strong intermolecular H-bonding.

On the basis of proton orientations whether protons attached to chiral carbon are closer to the carbonyl functionality or away from carbonyl group, the symmetrical diastereoisomers **14b** and **14c** can be distinguished as *syn*-symmetrical (s-s) or one is *anti*-symmetrical (a-s), respectively. As in s-s isomer protons were placed in deshielding zone of the carbonyl group and appears in downfield while in a-s isomer they appeared at a relatively up field (Fig. 3).[19]

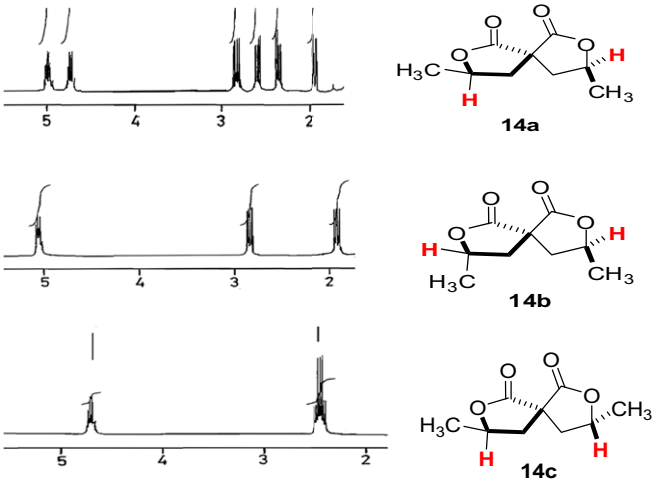


Fig. 3. ^{1}H NMR spectra of three diastereomers (**14a**–**c**) (methyl protons are not shown in Fig. 3).

Among the three lactones, unsymmetrical bis-spirolactone (**14a**) was selected for X-ray diffraction studies. These results confirmed the formation of spirolactones as well as the stereochemistry of the compound **14a** with space group $P4_12_12$, which is shown in Fig. 4.

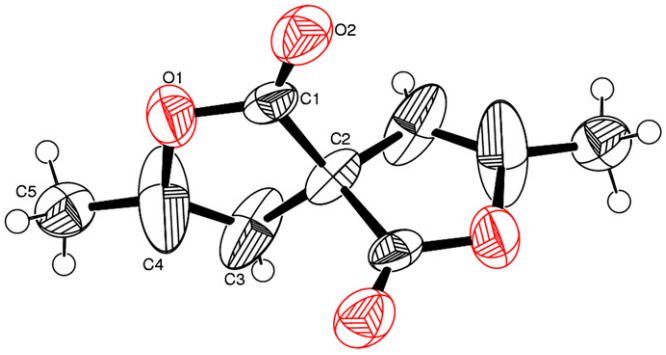
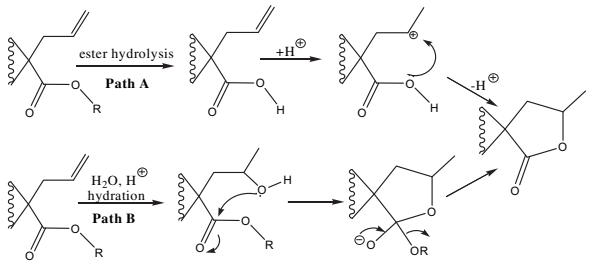


Fig. 4. X-ray crystal structure of spirolactone **14a** (unsymmetrical) and its ellipsoid plot.

A possible mechanism for lactonization reaction is shown in Scheme 5. Similarly, under the same reaction conditions the compound **9**, where three olefinic moieties and two ester moieties are present, hydroxylation of one of the residual olefinic moiety was observed along with bis-lactonization. These observations indicate that the reaction may proceed by path B. Since there was no indication of diacid formation during the course of reaction, lactone formation via path A is less likely to happen. Therefore, it can be suggested that, under the reaction conditions employed, hydration of the double bond might be faster than lactomerization (Scheme 5).



Scheme 5. Probable mechanism for formation of lactones in presence of mineral acid.

In conclusion, we have demonstrated a simple methodology for spirolactonisation of diesters **9** and **13** by mineral acid.

3. Experimental section

3.1. General

Reactions involving organometallic species were carried out under nitrogen by using oven-dried glassware and syringes. THF and Et_2O were distilled from sodium/benzophenone under nitrogen immediately prior to use. Dichloromethane was distilled over P_2O_5. TLC was performed by using (10×5 cm) glass plates coated with Acme's silica gel GF_{254} (containing 13% calcium sulfate as a binder). Flash-column chromatography was performed by using Aceme silica gel (100–200 mesh). Solvents were concentrated at reduced pressure on a Buchi R-114 rotary evaporator. ^{1}H NMR (400 MHz) and ^{13}C NMR (75.1 MHz) spectra were recorded at room temperature on AX 400 with TMS (δ=0.0 ppm, ^{1}H NMR spectra) and $CDCl_3$ (δ=77.0 ppm, ^{13}C NMR spectra) as internal standards. IR spectra were recorded on a Nicolet Impact-400 FTIR spectrometer. Accurate mass measurements were determined on a Micromass Q-Tof spectrometer.

*3.1.1. Dimethyl 2,3-diallylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**9**).* To a cooled solution (at 0 °C) of dimethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **8** (600 mg, 2.85 mmol) in THF (10 mL) was added NaHMDS (1 M solution in hexane) (8.57 mL, 8.57 mmol) in a drop-wise manner. After half an hour when the color of the solution became red allyl bromide (0.97 mL, 11.48 mmol) was added slowly at 0 °C. At the conclusion of the reaction (TLC monitoring, 10 h), reaction mixture was quenched with aq saturated NH_4Cl solution (2 mL) and the solvent was evaporated under reduced pressure. The residue was partitioned between water (50 mL) and ether (25 mL). The aqueous portion was extracted with ether (3×25 mL). Combined organic portion was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the resulting residue was purified by a silica gel column chromatography (6% ethyl acetate/petroleum ether) to deliver **9** (663 mg, 73%) as a white crystalline solid. Mp: 125–126 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.67 (dd, J_1=12.8 Hz, J_2=7.7 Hz, 1H), 1.7 (1/2 AB q, J=9.5 Hz, 2H), 2.03 (dd, J_1=13.2 Hz, J_2=8.0 Hz, 1H), 2.82–3.07 (m, 4H), 3.65 (s, 3H), 3.75 (s, 3H), 4.98–5.07 (m, 4H), 5.52–5.65 (m, 2H), 6.05 (dd, J_1=8.8 Hz, J_2=3.1 Hz, 1H), 6.48 (dd, J_1=8.6 Hz, J_2=3.1 Hz, 1H) ppm, ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 40.2, 41.3, 45.5, 47.8, 48.5, 51.5, 51.8, 61.5, 61.7, 117.8, 118.6, 133.7, 134.1, 134.4, 140.6, 173.9, 175.0 ppm, IR (KBr): ν_{max} 2917, 1760, 1540, 1255 cm^{-1}, HRMS (QTOF ES$^+$): m/z calcd for $C_{17}H_{23}O_4$: 291.1596; found: 291.1602 $[M+H]^+$.

*3.1.2. Bis-lactonization of dimethyl 2,3-diallylbicyclo dicarboxylate (**11**).* A mixture of dimethyl 2,3-diallylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **9** (300 mg, 1.03 mmol) and concd H_2SO_4 (5 mL) was stirred at 70 °C. At the conclusion of the reaction (TLC monitoring, 2.5 h), reaction was quenched with aq saturated $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3×25 mL),

combined organic layer was washed with water followed by brine. The solvent was evaporated under reduced pressure and the resulting residue was purified by a silica gel column chromatography (20% ethyl acetate/petroleum ether) to deliver **11** (188 mg, 65%) as a white crystalline solid (space group *P*−1, crystallization solvent: ethyl acetate/petroleum ether). The details of this X-ray crystallographic data of compound **11** have also been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC-780702. Mp: 155–158 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J=5.8 Hz, 3H), 1.38 (dd, J_1=17.2 Hz, J_2=11.3 Hz, 2H), 1.41 (d, J=6.2, 3H), 2.05–2.14 (m, 4H), 2.29 (dd, J_1=11.2 Hz, J_2=5.5 Hz, 1H), 2.56 (s, 1H), 2.73 (d, J=11.7 Hz, 1H), 3.31 (br s, 1H), 3.40–3.41 (m, 1H), 3.8–3.9 (m, 1H), 4.46–4.53 (m, 1H), 4.80–4.83 (m, 1H) ppm, ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.8, 25.0, 34.0, 34.5, 37.3, 38.2, 44.5, 51.9, 54.1, 55.3, 65.4, 73.9, 79.7, 176.0, 180.7 ppm, IR (KBr): ν_{max} 1760, 1442, 1256 cm^{-1}, HRMS (QTOF ES$^+$): m/z calcd for $C_{15}H_{21}O_5$: 281.1389; found: 281.1402 $[M+H]^+$.

*3.1.3. Bis-lactonization of diethyl 2,2-diallylmalonate (**14a**–**c**).* A mixture of diethyl 2,2-diallylmalonate **13**[17] (500 mg, 2.08 mmol) and concd H_2SO_4 (11 mL) was stirred at 70 °C. At the conclusion of the reaction (TLC monitoring, 2.5 h), the reaction mixture was quenched with aq saturated $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate (3×25 mL), combined organic layer was washed with water followed by brine. The solvent was evaporated under reduced pressure and the resulting residue was purified by a silica gel column chromatography (15–25% ethyl acetate/petroleum ether) to give **14a** (150 mg), **14b** (73 mg), and **14c** (75 mg) in 2:1:1 ratio as a white crystalline solid. The overall yield is 78%. The X-ray crystallographic details of compound **14a** have also been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC-780703 (space group $P4_12_12$, crystallization solvent: ethyl acetate/petroleum ether), compound **14a**: mp: 118–119 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (d, J=6.1 Hz, 3H), 1.5 (d, J=6.4 Hz, 3H), 1.92 (dd, J_1=12.9 Hz, J_2=9.8 Hz, 1H), 2.34 (dd, J_1=13.4 Hz, J_2=6.7 Hz, 1H) 2.60 (dd, J_1=13.1 Hz, J_2=8.0 Hz, 1H), 2.82 (dd, J_1=12.8 Hz, J_2=5.8 Hz, 1H), 4.6–4.7 (m, 1H), 4.9–5.0 (m, 1H) ppm, ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6, 21.1, 39.7, 41.6, 54.0, 75.1, 76.1, 173.6, 173.9 ppm, IR (KBr): ν_{max} 3054, 2986, 2305, 1758, 1420, 1266 cm^{-1}, HRMS (QTOF ES$^+$): m/z calcd for $C_9H_{13}O_4$: 185.0814; found: 185.0814 $[M+H]^+$. Compound **14b**: mp: 117–118 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (d, J=6.1 Hz, 6H), 1.85 (dd, J_1=12.8 Hz, J_2=9.4 Hz, 2H), 2.83 (dd, J_1=12.8 Hz, J_2=5.8 Hz, 2H), 5.02–5.07 (m, 2H) ppm, ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.0, 40.6, 54.1, 76.0, 173.6 ppm, IR (KBr): ν_{max} 3058, 2985, 2306, 1757, 1449, 1267 cm^{-1}, compound **14c**: mp: 115–118 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.5 (d, J=6.4 Hz, 6H), 2.3–2.5 (m, 4H), 4.6–4.7 (m, 2H) ppm, ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.0, 40.8, 53.4, 75.6, 174.4 ppm, IR (KBr): ν_{max} 1761, 1445, 1266 cm^{-1}.

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