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Solvent Effect in Reactions Using Stryker's Reagent

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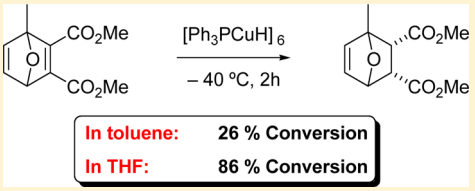
Supporting Information

ABSTRACT: The solvent has a significant influence in the rate of reactions promoted by Stryker's reagent. The reactions performed in THF were, in most cases, faster than in toluene.



We have recently developed some studies on the use of Stryker's reagent[1,2] for transforming natural furanoheliangolides (**1**) into eremantholides (**2**) (Scheme 1).[3,4] In the course of this research we observed that the presence of an allylic oxygen at C-15 of the substrates produced two remarkable and rather unexpected changes: (1) the reactions became faster, and (2) the reagent lost a part of its chemoselectivity. We rationalized these changes as being the result of a possible complexation of Stryker's reagent with the allylic oxygenated function (alcohol, ester, or ether) at C-15, which could enhance the reactivity of the reagent and, by forcing the proximity with the conjugate furanone system, could also result in reduction of this system.

We have thus decided to perform some reactions comparing the behavior of the Stryker's reagent in toluene and in tetrahydrofuran (THF). Toluene, the usual solvent for these reactions,[5−16] is the solvent that we have used in our previous studies; THF is an oxygenated solvent and could, possibly, form complexes with the reagent thus enhancing its reactivity and modifying its selectivity.[17] In the present paper we report the results of this research.

As substrates for our first set of experiments we have chosen some natural furanoheliangolides and simple derivatives that we have used before. Due to a considerable difference in the reactivity, they were separated in two groups according to the oxygenation at C-15 (R_2 = H or R_2 = OR′, Scheme 1). The reaction conditions were the same (25 °C, 0.5 mol of reagent for each mol of substrate) except for the reaction time: 2 h for the less reactive substrates (the 15-non-oxygenated compounds **3**−**5**) (results summarized in Table 1) and 30 min for the more reactive 15-oxygenated compounds **6** and **7** (results summarized in Table 2).

It is clear, from the results in Tables 1 and 2, that the use of THF produces a considerable increase in the reaction rates of the 15-non-oxygenated substrates (**3**, **4**, and **5**) but does not make any significant change in the reactions of the 15-oxygenated substrates (**6** and **7**). It seems that the oxygenated function in C-15 of substrates **6** and **7** already produces the maximum possible enhancement of the rate of the reactions, and thus the change of the solvent has no effect on these reactions. It is also noteworthy that for **3**, **4**, and **5** both the reduction (as measured by the consumption of starting material) and the cyclization (as measured by the ratio between cyclized to noncyclized products) reactions were affected, resulting in formation of larger amounts of eremantholides (**8**, **10**, and **12**).

In Table 2 we can also note that the change of solvent has no effect on the chemoselectivity of the reagent. In products **14** and **16** only the α-methylene lactone was reduced, whereas in products **15** and **5** reduction of the system conjugated with the furanone occurred. We can see in the table that the use of THF has no effect on the ratio of the products.

An additional observation, the formation of **5** in the reduction of **7**, is rather surprising because our results show that the α-methylene lactone is usually the most reactive group of these substrates. In fact, as can be seen in Table 1, **5** can be easily reduced by the Stryker's reagent: in the reduction of **7**, it is possible that **5** has withstood reduction because it was in its enolate form.

We have extended these studies to two other non-natural substrates (**17** and **18**), which we had already reduced with Stryker's reagent as part of other related research.

The reactions depicted in Scheme 2 were carried out in toluene and in THF with 0.5 mol of reagent for each mole of substrate, but we had to vary the temperatures and the time of reaction due to differences in reactivity of the substrates. The results are summarized in Table 3.

We can observe in Table 3 that **18** is reduced very easily at room temperature; the starting material was 100% consumed in

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Scheme 1. Conjugate Reduction Followed by Cyclization

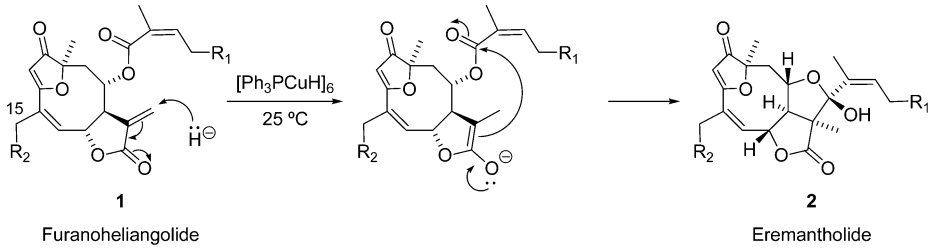
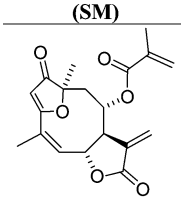
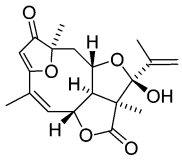
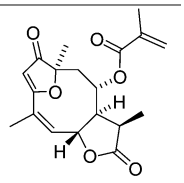
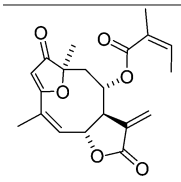
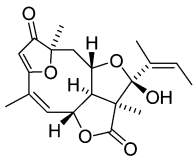
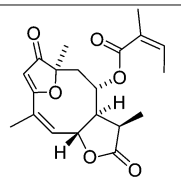
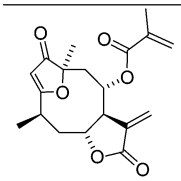
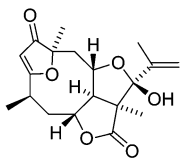
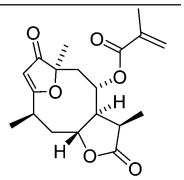


Table 1. Solvent Effects in Reactions of 15-Non-oxygenated Furanoheliangolides; Reaction Time 2 h

Starting Material (SM)	Solvent	Consumed SM	Products and yields*	
			 + 	
3			**8**	**9**
	Toluene	87 %	49 %	36 %
	THF	100 %	92 %	–
			 + 	
4			**10**	**11**
	Toluene	75 %	15 %	63 %
	THF	100 %	52 %	36 %
			 + 	
5			**12**	**13**
	Toluene	100 %	65 %	27 %
	THF	100 %	93 %	–

*All yields in this paper were calculated on the basis of the amount of starting material that was consumed.

both cases. However, with THF both possible stereoisomers were formed in an almost 1:1 ratio, indicating lower stereoselectivity consistent with higher reactivity. At −40 °C the stereoselectivity was 100% for both conditions, and from the consumed starting material, the greater reactivity in THF is evident.

Substrate **17** is reduced at a moderate rate, but the cyclization of the intermediate enolate to afford **19** is relatively slow leading to the formation of a predominance of **20** on workup. From the consumed starting material we can see that THF produces an increase in the rate of the reduction, but from the ratio of cyclized to noncyclized products it is clear that THF has no effect in the rate of the cyclization.

In conclusion, we can say that THF is, in general, a better solvent than toluene for reactions with Stryker's reagent. In most cases the rate of the reactions is higher in THF and the chemoselectivity is not affected. In one case, however, the increase in the rate resulted also in reduction of stereoselectivity.

EXPERIMENTAL SECTION

Materials and Methods. Reagents and starting materials were purchased from commercial sources and used as received or were synthesized when convenient. Natural products starting materials were isolated from natural sources as described in the literature. If necessary, solvents were purified following standard literature procedures. The reactions were carried out under an atmosphere of argon as specified in the experimental procedures. The NMR spectra were recorded using a 500 MHz instrument (500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR) or a 400 MHz instrument (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR); $CDCl_3$ and mixtures of $CDCl_3$ and DMSO-d_6 were used as solvent with TMS as internal standard. High resolution mass spectra (HRMS) were obtained on an ESI-TOF mass spectrometer. TLC was performed on precoated silica gel 60 plates (0.25 mm thick), and silica gel 60 (70−230 mesh) was used for column chromatography.

General Procedure for Reduction with Stryker's Reagent. A 9.5×10^{-3} M solution of the substrate (n mmol, 0.047 mmol < n < 0.091 mmol) in toluene or THF and recently prepared[3,18] Stryker's reagent ($n/2$ mmol), were mixed together forming an homogeneous solution that was stirred at room temperature or −40 °C for the time specified in the text. The reaction was quenched with saturated

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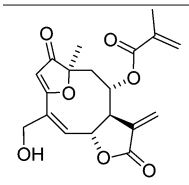
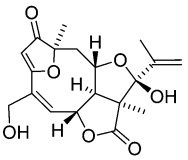
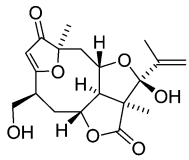
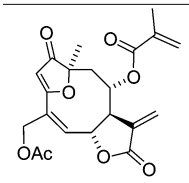
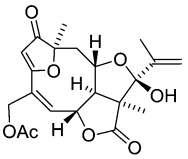
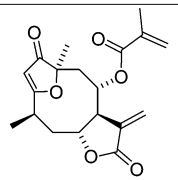
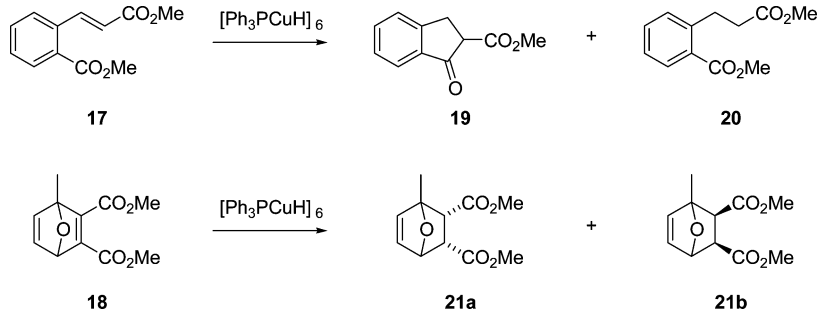
Table 2. Solvent Effects in Reactions of 15-Oxygenated Furanoheliangolides; Reaction Time 30 min

SM	Solvent	Consumed SM	Products and yields	
			 + 	
6			**14**	**15**
	Toluene	62 %	45 %	39 %
	THF	67 %	46 %	40 %
			 + 	
7			**16**	**5**
	Toluene	100 %	26 %	59 %
	THF	100 %	25 %	64 %

Scheme 2. Reduction of Non-natural Substrates



17 **19** **20**

18 **21a** **21b**

Table 3. Solvent Effects in Reactions of Non-natural Substrates 17 and 18

SM	temp (°C)	time (h)	solvent	consumed SM (%)	products and yields (%)	
17	25	0.5	toluene	53	**19**, 22	**20**, 67
			THF	76	**19**, 23	**20**, 69
18	25	2	toluene	100	**21a**, 88	
			THF	100	**21a**, 47	**21b**, 43
18	−40	2	toluene	26	**21a**, 91	
			THF	86	**21a**, 90	

ammonium chloride solution. The mixture was stirred for 1 h. During this period a white precipitate was formed. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel.

(2aS,3R,4aS,6R,11aR,11bR)-3-Hydroxy-3-isopropenyl-2a,6,10-trimethyl-2a,3,5,6,11a,11b-hexahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalene-2,7(4aH)-dione (Eremantholide C)[3] ***(8)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. White solid: mp (229−230 °C), 8.6 mg, 49% yield (toluene); 18.4 mg, 92% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.19 (3H, s); 1.49 (3H, s); 1.90 (3H, dd, J = 1.5, 0.9 Hz); 2.06 (1H, dd, J = 13.6, 11.9 Hz); 2.06 (3H, dd, J = 2.4, 1.6 Hz); 2.41 (1H, dd, J = 13.6, 2.6 Hz); 2.57 (1H, br.s); 2.85 (1H, dd, J = 7.0, 4.2 Hz); 4.14 (1H, dddd, J = 11.9, 4.2, 2.6, 0.6 Hz); 4.98 (1H, dddq, J = 7.0, 2.7, 2.4, 0.6 Hz); 5.08 (1H, dd, J = 2.0, 1.5 Hz); 5.33 (1H, dd, J = 2.0, 0.9 Hz); 5.62 (1H, s); 6.03 (1H, dq, J = 2.7, 1.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 18.9, 20.3, 20.6, 21.9, 43.7, 59.8, 62.5, 78.5, 81.5, 89.9, 104.5, 106.2, 116.1, 130.2, 134.6, 142.0, 175.4, 186.8, 205.2.

(3R,3aR,4S,6R,11aR)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,11a-octahydro-6,9-epoxycyclodeca[b]furan-4-yl 2-Methylacrylate[3] ***(9)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. Colorless oil: 6.3 mg, 36% yield (toluene). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.34 (3H, d, J = 6.7 Hz); 1.50 (3H, s); 1.91 (3H, dd, J = 1.45, 0.8 Hz); 2.12 (3H, dd, J = 2.4, 1.7 Hz); 2.19 (1H, dd, J = 13.4, 1.4 Hz); 2.35 (1H, dd, J = 13.4, 11.6 Hz); 2.40 (1H, dq, J = 11.6, 6.7 Hz); 3.00 (1H, ddd, J = 11.6, 9.2, 2.2 Hz); 4.92 (1H, dddd, J = 11.6, 2.2, 1.4, 0.6 Hz); 5.05 (1H, dddq, J = 9.2, 2.9, 2.4, 0.6 Hz); 5.63 (1H, q, J = 1.4 Hz); 5.78 (1H, s,); 5.99 (1H, dq, J = 2.9, 1.7 Hz); 6.09 (1H, dq, J = 1.4, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.4, 18.1, 20.5, 21.6, 38.4, 44.8, 55.2, 67.9, 80.3, 88.9, 105.1, 126.9, 128.6, 133.2, 135.3, 166.3, 176.6, 186.8, 203.9.

(2aS,3R,4aS,6R,11aR,11bR)-3-Hydroxy-2a,6,10-trimethyl-3-[(1Z)-1-methylprop-1-en-1-yl]-2a,3,5,6,11a,11b-hexahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalene-2,7(4aH)-dione[3] ***(10)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. Colorless oil: 2.3 mg, 15% yield (toluene); 10.5 mg, 52% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.17 (3H, s); 1.42 (3H, s); 1.70−1.71 (3H, m); 1.76 (3H, br.s); 1.97−2.02 (4H, m); 2.39 (1H, dd, J = 13.6, 2.4 Hz); 2.75 (1H, dd, J = 7.2, 4.4 Hz); 2.88 (1H, br.s); 4.07−4.09 (1H, m); 4.90−4.91 (1H, m); 5.25−5.55 (2H, m); 5,96 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.3, 20.3, 20.5, 21.4, 21.9, 43.7, 61.2, 62.0, 78.9, 81.4, 90.0, 104.5, 127.9, 130.1, 131.7, 134.8, 175.6, 187.0, 205.4.

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(3R,3aR,4S,6R,11aR)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,11a-octahydro-6,9 epoxycyclodeca[b]furan-4-yl (2Z)-2-Methylbut-2-enoate[3] ***(11)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. Yellow oil: 9.5 mg, 63% yield (toluene); 7.2 mg, 36% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.26 (3H, d, J = 7.0 Hz); 1.44 (3H, s); 1.78 (3H, s); 1.91 (3H, d, J = 7.0 Hz); 2.05 (3H, s); 2.10−2.13 (1H, m); 2.26−2.33 (2H, m); 2.89−2.94 (1H, m); 4.85−4.87 (1H, m); 5.02−5.04 (1H, m); 5.71 (1H, s); 5.93 (1H, br.s); 6.10−6.15 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.4, 15.9, 20.3, 20.5, 21.6, 38.4, 44.9, 55.1, 67.1, 80.4, 89.0, 105.1, 133.2, 141.6, 166.6, 176.8, 187.0, 204.2.

(2aS,3R,4aS,6R,10R,11aR)-3-Hydroxy-3-isopropenyl-2a,6,10-trimethyl-2a,3,5,6,10,11,11a,11b-octahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalene-2,7(4aH)-dione[19] ***(12)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. Colorless oil: 13.1 mg, 65% yield (toluene); 18.7 mg, 93% yield (THF). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.21 (1H, br.s); 1.37 (3H, br.s); 1.45 (3H, s); 1.90 (3H, br.s); 2.03 (1H, dd, J = 13.4, 11.9 Hz); 2.13−2.17 (1H, m); 2.41−2.45 (2H, m); 2.57 (1H, dd, J = 6.7, 4.4 Hz); 2.99−3.03 (1H, m); 3.99 (1H, ddd, J = 11.9, 4.4, 2.2 Hz); 4.21−4.26 (1H, m); 5.06−5.07 (1H, m); 5.32 (1H, br.s); 5.61 (1H, br.s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.9, 19.2, 21.4, 22.9, 31.2, 41.5, 44.3, 60.3, 66.9, 77.2, 79.9, 90.3, 104.5, 106.7, 116.3, 142.2, 176.0, 193.8, 206.0.

(3R,3aS,4S,6R,10R,11aR,11bR)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,10,11,11a- decahydro-6,9-epoxycyclodeca[b]furan-4-yl 2-Methylacrylate[3] ***(13)***. Purified by column chromatography in silica gel using a 9:1 mixture of toluene/ethyl acetate as eluent. Colorless oil: 5.4 mg, 27% yield (toluene). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.33 (3H, d, J = 6.7 Hz); 1.42 (3H, d, J = 7.3 Hz); 1.45 (3H, s); 1.91 (3H, br.s); 2.16−2.40 (5H, m); 2.50−2.55 (1H, m); 3.06−3.08 (1H, m); 4.37−4.40 (1H, m); 4.77−4.80 (1H, m); 5.62 (1H, br.s); 5.73 (1H, br.s); 6.07 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 16.0, 16.1, 18.1, 20.7, 31.3, 38.5, 41.5, 46.5, 59.4, 68.2, 79.2, 88.4, 104.8, 126.9, 135.4, 166.3, 177.1, 194.1, 204.9.

(2aS,3R,4aS,6R,11aR,11bR)-3-Hydroxy-10-(hydroxymethyl)-3-isopropenyl-2a,6-dimethyl-2a,3,5,6,11a,11b-hexahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalene-2,7(4aH)-dione (15-Hydroxy-eremantholide C)[3] ***(14)***. Purified by column chromatography in silica gel using a 1:1 mixture of hexane/ethyl acetate as eluent. Colorless oil: 5.4 mg, 45% yield (toluene); 6.0 mg, 46% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.20 (3H, s); 1.50 (3H, s); 1.90 (3H, br.s); 2.05−2.10 (1H, m); 2.42 (1H, dd, J = 13.7, 2.3 Hz); 2.68 (1H, br.s); 2.91 (1H, dd, J = 7.3, 4.1 Hz); 4.17−4.19 (1H, m); 4.36−4.42 (2H, m); 5.05−5.06 (1H, m); 5.08 (1H, br.s); 5.33 (1H, br.s); 5.72 (1H, s); 6.31 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 19.1, 20.7, 21.8, 43.8, 62.1, 63.3, 78.3, 81.3, 90.1, 106.4, 106.8, 116.1, 116.2, 134.5, 135.3, 141.7, 175.3, 184.0, 205.0.

(2aS,3R,4aS,6R,10S,11aR,11bR)-3-Hydroxy-10-(hydroxymethyl)-3-isopropenyl-2a,6-dimethyl-2a,3,5,6,10,11,11a,11b-octahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalene-2,7(4aH)-dione[3] ***(15)***. Purified by column chromatography in silica gel using a 1:1 mixture of hexane/ethyl acetate as eluent. Yellow oil: 4.7 mg, 39% yield (toluene); 5.2 mg, 40% yield (THF). ^{1}H NMR ($CDCl_3$ + 10% DMSO-d_6, 500 MHz) δ (ppm): 1.16 (3H, s); 1.44 (3H, s); 1.87 (3H, br.s); 2.04 (1H, dd, J = 14.0, 11.7 Hz); 2.24−2.31 (1H, m); 2.35 (1H, dd, J = 14.0, 2.3 Hz); 2.41−2.44 (1H, m); 2.54 (1H, dd, J = 6.7, 4.3 Hz); 2.99−3.04 (1H, m); 3.80 (1H, dd, J = 10.5, 6.4 Hz); 3.92 (1H, dd, J = 10.5, 6.7 Hz); 3.98−4.01 (1H, m); 4.32−4.36 (1H, m); 5.01 (1H, br.s); 5.26 (1H, br.s); 5.67 (1H, br.s); 5.71 (1H, br.s). ^{13}C NMR ($CDCl_3$ + 10% DMSO-d_6, 125 MHz) δ (ppm): 18.6, 20.7, 22.0, 36.0, 38.5, 43.7, 59.9, 60.8, 66.2, 75.9, 80.1, 88.5, 104.1, 105.8, 114.3, 142.2, 175.9, 190.4, 205.5.

[(2aS,3R,4aS,6R,11aR,11bR)-3-Hydroxy-3-isopropenyl-2a,6-dimethyl-2,7-dioxo-2a,3,4a, 5,6,7,11a,11b-octahydro-2H-6,9-epoxy-1,4-dioxacyclodeca[cd]pentalen-10-yl]methyl Acetate[3] ***(16)***. Purified by column chromatography in silica gel using a 8:2 mixture of toluene/ethyl acetate as eluent. Yellow oil: 5.0 mg, 26% yield (toluene); 4.8 mg, 25% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.19 (3H, s); 1.48 (3H, s); 1.88 (3H, br.s); 1.99−2.06 (1H, m); 2.10 (3H, s); 2.41 (1H, dd, J = 13.5, 2.5 Hz); 2.78 (1H, br.s); 2.89 (1H, dd, J = 7.1, 4.1 Hz); 4.10−4.17 (1H, m); 4.76 (2H, br.s); 5.02−5.07 (2H, m); 5.31 (1H, br.s); 5.70 (1H, s); 6.32−6.33 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 18.9, 20.5, 21.7, 22.7, 43.7, 59.7, 62.0, 63.5, 78.3, 81.2, 90.2, 106.2, 106.5, 116.2, 129.6, 138.0, 141.8, 170.2, 175.2, 183.1, 205.0.

(3aS,4S,6R,10R,11aR)-6,10-Dimethyl-3-methylene-2,7-dioxo-2,3,3a,4,5,6,7,10,11,11a-decahydro-6,9-epoxycyclodeca[b]furan-4-yl 2-Methylacrylate[3] ***(5)***. Purified by column chromatography in silica gel using a 8:2 mixture of toluene/ethyl acetate as eluent. Yellow oil: 9.8 mg, 59% yield (toluene); 10.6 mg, 64% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.36 (3H, d, J = 7.0 Hz); 1.42 (3H, s); 1.75 (3H, br.s); 2.05−2.07 (1H, m); 2.27−2.30 (1H, m); 2.38−2.43 (2H, m); 2.95−3.01 (1H, m); 3.28−3.30 (1H, m); 4.26−4.29 (1H, m); 4.42−4.45 (1H, m); 5.37−5.38 (1H, m); 5.46 (1H, br.s); 5.62 (1H, br.s); 5.93 (1H, br.s); 6.12 (1H, d, J = 3.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 16.5, 17.9, 21.2, 31.2, 41.4, 45.4, 54.7, 72.0, 80.2, 89.7, 104.7, 124.3, 126.4, 133.9, 135.6, 166.8, 168.9, 193.8, 205.1.

Methyl 1-Oxoindane-2-carboxylate[20] ***(19)***. Purified by column chromatography in silica gel using a 8:2 mixture of hexane/ethyl acetate as eluent. Yellow oil: 2.0 mg, 53% yield (toluene); 3.0 mg, 76% yield (THF). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.39 (dd, 1H, J_1 = 17.3, J_2 = 8.3 Hz); 3.58 (dd, 1H, J_1 = 17.3, J_2 = 3.8 Hz); 3.75 (dd, 1H, J_1 = 8.3, J_2 = 3.8 Hz); 3.80 (s, 3H); 7.41 (t, 1H; J = 7.5 Hz); 7.51 (d, 1H; J = 7.5 Hz); 7.64 (t, 1H; J = 7.5 Hz); 7.79 (d, 1H; J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 200.0, 169.6, 153.6, 135.4, 135.2, 127.8, 126.5, 124.7, 53.1, 52.8, 30.3.

Methyl 2-(3-Methoxy-3-oxopropyl)benzoate[21] ***(20)***. Purified by column chromatography in silica gel using a 8:2 mixture of hexane/ethyl acetate as eluent. Yellow oil: 7.1 mg, 67% yield (toluene); 10.6 mg, 69% yield (THF). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.66 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 7.27 (m, 2H)), 7.42 (m, 1H), 7.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.7, 35.4, 51.4, 51.8, 126.2, 129.0, 130.7, 130.9, 132.0, 142.2, 167.5, 173.3.

Dimethyl (2R,3S)-1-Methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate ***(21a)***. Purified by column chromatography in silica gel using a 7:3 mixture of hexane/ethyl acetate as eluent. Yellow oil: 17.8 mg, 88% yield (toluene at 25 °C); 10 mg, 47% yield (THF at 25 °C); 4.8 mg, 91% yield (toluene at −40 °C); 15.6 mg, 90% yield (THF at −40 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.60 (s, 3H); 3.0 (d,1H, J = 10.2 Hz); 3.53 (dd, 1H, J = 10.1, 4.5 Hz); 3.55 (s, 3H); 3.58 (s, 3H); 4.98 (dd, 1H, J = 4.6, 1.7 Hz); 6.33 (d, 1H, J = 5.7 Hz); 6.42 (dd, 1H, J = 1.7, 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 17.9, 50.7, 51.7, 51.7, 52.8, 79.5, 88.2, 135.0, 138.1, 170.7, 171.1. IR ν_{max} (liquid film): 2952, 1743, 1729, 1438, 712 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{11}H_{14}O_5Na^+$ (MNa+) 249.0739, found 249.0735.

Dimethyl (2S,3R)-1-Methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate ***(21b)***. Purified by column chromatography in silica gel using a 7:3 mixture of hexane/ethyl acetate as eluent. Yellow oil: 9 mg, 43% yield (THF). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.52 (s, 3H); 2.77 (d, 1H, J = 8.9 Hz); 2.87 (d, 1H, J = 9.1 Hz); 3.62 (s, 3H); 3.64 (s, 3H); 5.31 (d, 1H, J = 1.7 Hz); 6.16 (d, 1H, J = 5.6 Hz); 6.40 (dd, 1H, J = 5.6, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 15.7, 49.9, 50.5, 51.9, 52.1, 79.2, 87.9, 137.2, 139.8, 171.7, 171.8. IR ν_{max} (liquid film): 2952, 1742, 1729, 1435 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{11}H_{14}O_5Na^+$ (MNa+) 249.0739, found 249.0733.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C spectra of compounds **12**, **19**, **20**, **21a**, and **21b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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