Synthesis of Non-Racemic 1-Hydroxycycloalkene-1-carboxylic-Acid Derivatives by Metathesis of α,α-Dialkylated Glycolate Derivatives

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A particularly flexible general way to synthesize 1-hydroxycycloalkene-1-carboxylic-acid derivatives from 2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-one (**1**), a chiral equivalent of glycolic acid, is reported. The method is based on a double enolate alkylation of the glycolate derivative, followed by ring closing metathesis. A formal synthesis of (−)-quinic acid is reported to demonstrate the potential of this approach.

Introduction. – During the recent years, ring closing metathesis has emerged as an extremely useful tool for the synthesis of cyclic compounds of various sizes [1]. Recently, we have reported the preparation of the enantiomerically pure dioxolanone **1**, a chiral equivalent of glycolic acid [2]. Based on this chemistry, we report here the preparation of 1-hydroxycycloalkene-1-carboxylic acids by use of a sequence of enolate alkylation and olefin metathesis [1])[2])[3]). The formal synthesis of (−)-quinic acid is reported to illustrate the potential of the method.

Results and Discussion. – The preparation of dioxolanones **3** and **4** was performed *via* double alkylation of the chiral glycolate derivative **1** (*Scheme 1*). The dioxolanone **1** was first allylated by treatment with lithium diisopropylamide (LDA) and allyl bromide (= 3-bromoprop-1-ene) to afford **2** as a *trans*/*cis* 3:1 mixture of diastereoisomers[4])[5]). When **2** was deprotonated with LDA and alkylated with 4-iodobut-1-ene and propargyl bromide (= 3-bromoprop-1-yne), the alkylated products **3** and **4** were obtained as *trans*/*cis* 2:1 and 2.5:1 mixture of diastereoisomers. Attempts to use other bases (KHMDS and NaHMDS; HMDS = hexamethyldisilazanide) and cosolvents (HMPA (hexamethylphosphoric triamide) and DMPU (*N*,*N*′-dimethylpropyleneurea)) did not bring any enhancement of the stereoselectivity. This reaction merits some comments since the stereoselectivity of the second alkylation was not as high as

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[1]) These results have been presented as a poster during the '3rd Electronic Conference on Synthetic Organic Chemistry' (ECSOC-3, "http://www.mdpi.org/ecsoc-3.htm", Poster a0018).

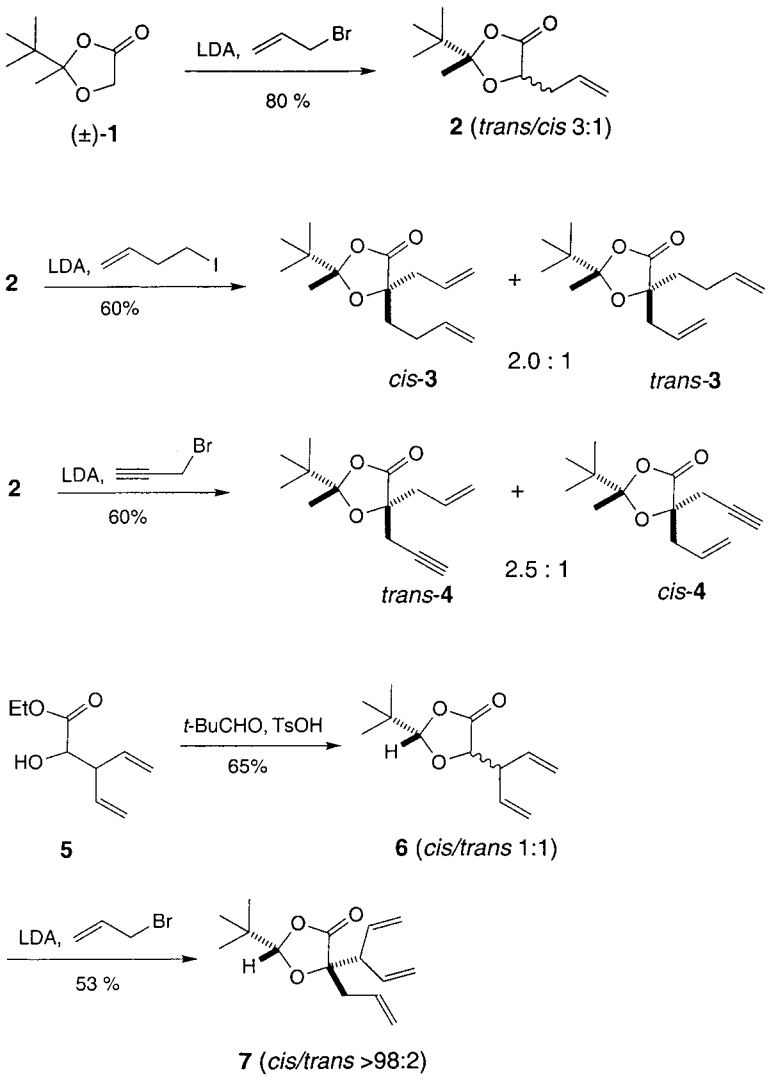
[2]) For a related preparation of 1-hydroxycyclopentane-1-carboxylic-acid derivatives *via* a radical pathway, see [3].

[3]) *Hammer* and *Undheim* have reported a similar approach for the synthesis of cyclic α-aminocarboxylic acids starting from a chiral glycine equivalent (*Schöllkopf* bislactim ether) *via* olefin ring closing metathesis [4]. A similar approach to cyclic amino acids *via* enyne metathesis has been recently reported [5].

[4]) The stereochemical outcome of the first alkylation gave also modest diastereoselectivities, this point will be discussed in detail in a forthcoming paper.

[5]) The *trans*/*cis* descriptors are describing the relative configuration of the *tert*-butyl group at C(2) and the largest (according to *CIP* rules) substituent at C(5).

Scheme 1



expected. Indeed, it has been reported by *Seebach* that alkylation of 2-(*tert*-butyl)-5-methyldioxolan-4-one occurs with very high stereoselectivity [6][7], and we have confirmed this observation in the 2-(*tert*-butyl)-2,4-dimethyldioxolanone series [2]. The modest stereochemical control observed here was attributed to the allylic 1,3-strain ($A^{1,3}$ strain) effect at the enolate level (*Fig.*). Indeed, to avoid repulsion with the *tert*-butyl group and to minimize $A^{1,3}$ strain, the vinyl moiety of the propenyl substituent is adopting the configuration depicted in model **A**, in which the vinyl group is *anti* to the *tert*-butyl substituent, and in which one of the two diastereotopic H-atoms is coplanar with the enolate moiety. The stereochemical outcome of the reaction is then controlled

by the antagonist steric effect of the *tert*-butyl and the vinyl groups. Related effects have been reported in enolate alkylations [8] and radical reactions [9]. *Kellog* has also observed a drop of selectivity during the alkylation of N,S-acetals from α-alkyl-α-thiocarboxylic acids when the α-alkyl group is a benzyl group; however, this observation remained unexplained [10]. This model was confirmed during the synthesis of **7**. Indeed compound **6**, which was prepared by acetalization of the corresponding α-hydroxy acid ethyl ester **5** with pivalaldehyde (=2,2-dimethylpropanal), was allylated in a totally stereoselective fashion[6]). This result is expected from the model discussed above since the enolate derived from **6** should adopt the conformation depicted in model **B** (*Fig.*). The two vinyl groups shield both faces of the enolate in a similar way. Therefore, the stereoselectivity is exclusively controlled by the acetal center (alkylation *anti* to the *tert*-butyl group, *ul* topicity) as in the *Seebach*'s case of lactic acid [7b].

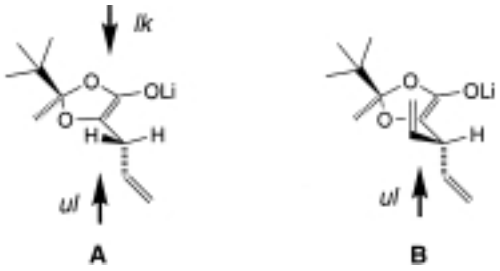


Figure. *Stereochemical models* **A** *and* **B** *for the alkylation of Li-enolates derived from* **2** *and* **6**, *respectively: effect of the adjacent prochiral center*

The three compounds **3**, **4**, and **7** were then treated with *Grubbs* catalyst **8** [2] to afford the spirocyclic derivatives **9**–**11** (*Scheme 2*). The cyclohexene derivative **9** was obtained in 90% yield when the reaction was run with 2 mol-% of catalyst at room temperature in benzene. As expected, a *cis*/*trans* 2.0:1 mixture of isomers was formed since *cis*/*trans*-**3** was used. Surprisingly, **10** was isolated in 65% yield as a single diastereoisomer when the reaction was performed in refluxing CH_2Cl_2 with 10 mol-% of catalyst and a *trans*/*cis* (2.5:1) mixture **4**[7]). The minor *cis* isomer was lost during this process by decomposition. Finally, the substrate **7** gave the vinylcyclopentene derivative **11** as a 60:40 mixture of diastereoisomers.

The utility of this approach was demonstrated by a formal synthesis of (−)-quinic acid (*Scheme 3*), a ubiquitous natural product that plays an important regulating role in the shikimate pathway[8]). Double alkylation of (*R*)-**1** (80% ee) gave the diene (2*R*,5*S*)-**3** in 51% yield after separation of the diastereoisomer by chromatography. The diene (2*R*,5*S*)-**3** afforded diastereoisomerically pure (2*R*,5*S*)-**9** in 94% yield upon treatment with 2 mol-% of **8**. Treatment of (2*R*,5*S*)-**9** with methanolic HCl gave the ester (*S*)-**12**, which was saponified and treated with Br_2 to afford the product of bromolactonization

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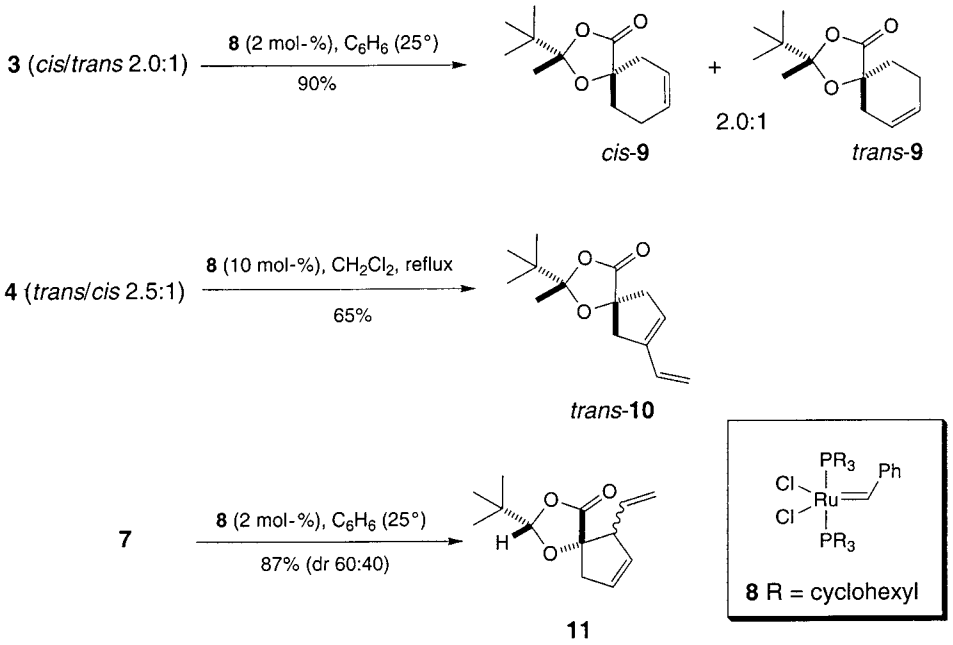
6) The alkylation was performed with pure *trans*-**6**. Attempts to deprotonate *cis*-**6** led mainly to decomposition products.

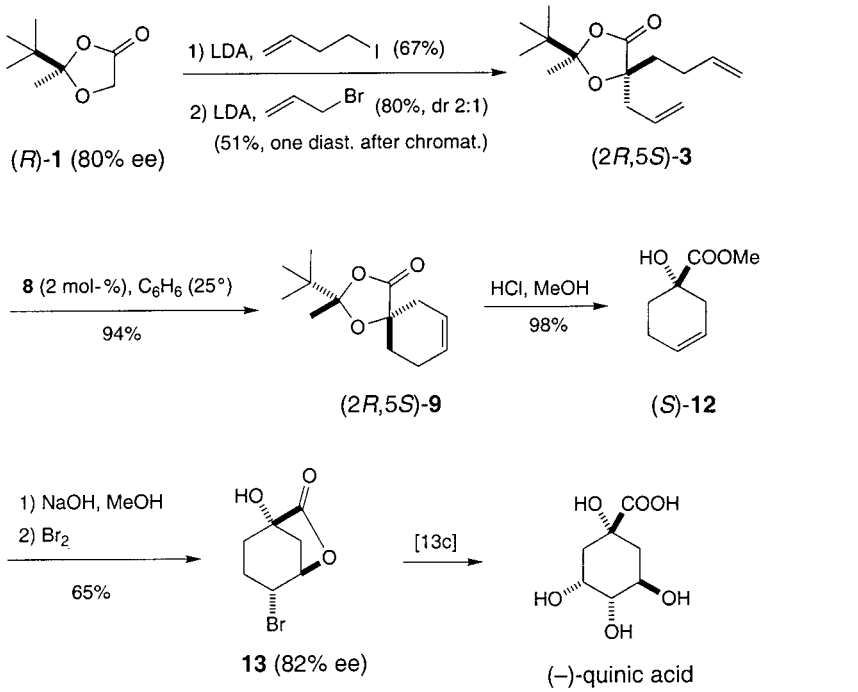
7) For early examples of enyne metathesis catalyzed by a tungsten carbene, see [11]. Ruthenium-catalyzed enyne metathesis has been reported; for pioneer examples, see [12].

8) For syntheses of racemic quinic acid, see [13]. For the synthesis of (−)-quinic acid, see [14]. Quinic acid has been widely applied as chiral building block for the synthesis of natural products; for a review, see [15].

Scheme 2



Scheme 3



13 (89% ee after one recrystallization). Conversion of **13** to (−)-quinic acid has already been reported [13c].

Conclusions. – We have presented here an efficient synthesis of cyclic non-racemic 1-hydroxycycloalkene-1-carboxylic-acid derivatives. The absolute configuration at C(1) can be preestablished by the choice of the starting enantiomer of **1** or by the sequence of the alkylations. This approach is particularly flexible and should be applicable to a wide range of biologically relevant compounds.

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Experimental Part

1. *General*. THF was freshly distilled from K under N_2, CH_2Cl_2 and benzene from CaH_2 under N_2. Flash column chromatography (FC): *Merck* silica gel *60* (70–230 mesh). Low-pressure flash chromatography (LP-FC): *Lobar®*, *Merck*, *LiChroprep Si 60* (40–63 μm). TLC: *Merck* silica gel *60 F_{254}* anal. plates; detection by UV, I_2, or spraying with a soln. of phosphomolybdic acid (25 g), $Ce(SO_4)\cdot 4H_2O$ (10 g), conc. H_2SO_4 soln. (60 ml), and H_2O (940 ml) with subsequent heating. GC: diastereoselectivity measurements by means of a column *Macherey-Nagel Optima-1701*, if not stated otherwise; enantiomer-excess measurements by means of a chiral column *6-TBDMS-2,3-DiAc γ-cyclodextrine, 65% cyclodextrine in OV 1701*. M.p.: not corrected; *Reicher Thermovar Kofler* hot-stage apparatus. IR Spectra: *Perkin-Elmer Mattson Unicam 500 16PC FT-IR*; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Gemini 200* (200 (^{1}H) and 50.3 MHz (^{13}C)), *Bruker AM 360* (360 (^{1}H) and 90.55 MHz (^{13}C)), *Bruker Avance DRX-500* (500 (^{1}H) and 125.76 MHz (^{13}C)); δ(H) in ppm rel. to $CHCl_3$ (= 7.26 ppm) and δ(C) in ppm rel. to $CDCl_3$ (= 77.0 ppm); coupling constants J in Hz in $CDCl_3$, unless otherwise stated; ^{13}C multiplicities by APT sequence. NOE: irradiated signal → affected signal (%). MS: *Vaccum Generators Micromass VG70/70E DS 11-250*; EI (70 eV), CI (CH_4) gas; in *m/z* (%); FAB: matrix 3-nitrobenzyl alcohol (NBA); Xe bombardment (8 kV, 1 mA).

2. *Lithium Diisopropylamide (LDA) Solution*. To a soln. of $(i\text{-}Pr)_2NH$ (14.1 ml, 0.1 mol) in THF (45.9 ml) at 0° under N_2, 2.5M BuLi in hexane (40.0 ml, 0.1 mol) was added, and the soln. was stirred for 10 min. This 1M LDA soln. was stored in a refrigerator and used within 2 weeks.

3. *Alkylation of* **1**: *General Procedure 1*. To 1M LDA (6.0 ml, 6.0 mmol) in THF (5.0 ml) containing HMPA (1.0 ml) at −78° under N_2, a soln. of **1** (790 mg, 5.0 mmol) in THF (5.0 ml) was added slowly. After stirring for 15 min, a soln. of the electrophile (5.0 mmol) in THF (5.0 ml) was added, and the soln. was allowed to warm up to r.t. within 2 h. Sat. $NaHCO_3$ soln. (10 ml) was added, the aq. layer was extracted with Et_2O (3 × 30 ml), the combined org. phase was washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. The crude mixture was purified by FC.

4. *(±)-2-(*tert*-Butyl)-2-methyl-5-(prop-2-enyl)-1,3-dioxolan-4-one* (**2**). According to *GP 1*, from (±)-**1** (790 mg, 5.0 mmol), LDA (10.0 ml, 10.0 mmol), and 3-bromoprop-1-ene (1.20 g, 10.0 mmol). FC (AcOEt/hexane, 1:20) gave *trans*/*cis*-**2** 3:1 (804 mg, 81%). IR (Film): 2978, 2966, 1795, 1380, 1253, 1211, 1151, 953. CI-MS: 199 (100, $[M+1]^+$), 141 (22), 101 (12), 99 (16), 83 (38). Anal. calc. for $C_{11}H_{18}O_3$ (198.27): C 66.64, H 9.15; found: C 66.28, H 9.43.

trans-**2**: ^{1}H-NMR (360 MHz): 5.78 (*m*, C*H*=CH$_2$); 5.13 (*m*, CH=C*H*$_2$); 4.4 (*dd*, *J* = 4.9, 6.2, H−C(5)); 2.48 (*m*, C*H*$_2$CH=CH$_2$); 1.45 (*s*, Me); 0.99 (*s*, *t*-Bu). NOE (500 MHz): 4.4 (H−C(5)) → 0.99 (6.2%); 1.45 (Me) → 2.48 (1.0%); 0.99 (*t*-Bu) → 4.4 (1.0%). ^{13}C-NMR (50.3 MHz): 172.6 (*s*); 131.9 (*d*); 119.1 (*t*); 116.2 (*s*); 75.6 (*d*); 40.1 (*s*); 36.9 (*t*); 24.3 (*q*); 22.5 (*q*).

cis-**2**: ^{1}H-NMR (360 MHz): 5.8 (*m*, C*H*=CH$_2$); 5.2 (*m*, CH=C*H*$_2$); 4.37 (*dd*, *J* = 4.5, 8, H−C(5)); 2.5 (*m*, C*H*$_2$CH=CH$_2$); 1.46 (*s*, Me); 0.94 (*s*, *t*-Bu). ^{13}C-NMR (50.3 MHz): 172.4 (*s*); 132.3 (*d*); 118.4 (*t*); 115.3 (*s*); 73.1 (*d*); 37.8 (*s*); 35.2 (*t*); 24.3 (*q*); 19.1 (*q*).

5. *(±)-5-(But-3-enyl)-2-(*tert*-butyl)-2-methyl-5-(prop-2-enyl)-1,3-dioxolan-4-one* (**3**). According to *GP 1*, from *trans/cis* **2** 3:1 (428 mg, 2.16 mmol), LDA (4.32 ml, 4.32 mmol) and 4-iodobut-1-ene (786 mg, 4.32 mmol). FC (Et_2O/hexane 1:20) gave *cis*/*trans*-**3** 2:1 (390 mg, 60%). IR (Film): 3080, 2079, 2879, 1790, 1643, 1485, 1379, 1153, 1068, 997, 929. CI-MS: 253 (34, $[M+1]^+$), 167 (58), 153 (58), 135 (82), 125 (61), 101 (38), 83 (100), 55 (68). Anal. calc. for $C_{15}H_{24}O_3$ (252.36): C 71.39, H 9.59; found: C 71.41, H 9.76.

trans-**3**: ^{1}H-NMR (500 MHz): 5.85–5.69 (*m*, 2 C*H*=CH$_2$); 5.20–5.02 (*m*, CH=C*H*$_2$); 4.96 (*dq*, *J* = 17.1, 1.7, 1 H, CH=C*H*$_2$); 4.90 (*dq*, *J* = 10.1, 1.7, 1 H, CH=C*H*$_2$); 2.51 (*m*, C*H*$_2$CH=CH$_2$); 2.28–2.26 (*m*, 1 H, CH$_2$C*H*$_2$CH=CH$_2$); 2.14–2.06 (*m*, 1 H, CH$_2$C*H*$_2$CH=CH$_2$); 1.82 (*ddd*, *J* = 14, 11.9, 4.9, C*H*$_2$CH$_2$); 1.72 (*ddd*, *J* = 14.0, 12.1, 4.9, C*H*$_2$CH$_2$); 1.49 (*s*, Me); 0.94 (*s*, *t*-Bu). NOE (500 MHz): 2.51 (C*H*$_2$CH=CH$_2$) → 1.49 (0.72%); 1.82 (C*H*$_2$CH$_2$) → 0.94 (1.8%); 1.72 (C*H*$_2$CH$_2$) → 0.94 (2.3%); 1.49 (Me) → 2.51 (0.95%); 0.95 (*t*-Bu) → 1.82 (0.14%), 1.72 (0.45). ^{13}C-NMR (125.76 MHz): 175.1 (*s*); 137.8 (*d*); 131.9 (*d*); 119.8 (*t*); 115.3 (*t*); 115.1 (*s*); 81.0 (*s*); 40.9 (*t*); 39.1 (*s*); 34.9 (*t*); 27.2 (*t*); 25.2 (*q*); 23.4 (*q*).

cis-**3**: ^{1}H-NMR (500 MHz): 5.93–5.73 (*m*, 2 C*H*=CH$_2$); 5.20–5.15 (*m*, CH=C*H*$_2$); 4.95 (*m*, CH=C*H*$_2$); 2.58–2.52 (*m*, C*H*$_2$CH=CH$_2$); 2.34–2.24 (*m*, CH$_2$C*H*$_2$CH=CH$_2$); 2.20–2.10 (*m*, CH$_2$C*H*$_2$CHCH$_2$); 1.92–1.75 (*m*, C*H*$_2$CH$_2$); 1.55 (*s*, Me); 1.05 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 175.1 (*s*); 137.6 (*d*); 131.7 (*d*); 119.7 (*t*); 115.4 (*t*); 113.1 (*s*); 80.9 (*s*); 41.0 (*s*); 39.9 (*t*); 35.9 (*t*); 27.6 (*t*); 25.2 (*q*); 23.3 (*q*).

6. *2-(*tert*-Butyl)-2-methyl-5-(prop-2-enyl)-5-(prop-2-ynyl)-1,3-dioxolan-4-one* (**4**). According to *GP 1*, from (±)-**1** (400 mg, 2.01 mmol), LDA (4.04 ml, 4.04 mmol), and 3-bromoprop-1-yne (478 mg, 4.02 mmol). FC (Et$_2$O/hexane, 1:20) gave *trans*/*cis*-**4** 2.5:1 (280 mg, 70%). IR (Film): 3295, 2978, 2920, 2880, 1790, 1485, 1381, 1285, 1153, 925. CI-MS: 237 (50, [*M* + 1]$^+$), 179 (57), 151 (27), 137 (33), 109 (18); 101 (52), 83 (29), 69 (100), 57 (50). Anal. calc. for $C_{14}H_{20}O_3$ (236.14): C 71.16, H 8.53; found: C 71.24, H 8.52.

trans-**4**: ^{1}H-NMR (500 MHz): 5.92–5.80 (*m*, C*H*=CH$_2$); 5.27–5.21 (*m*, CH=C*H*$_2$); 2.68 (*d*, *J* = 2.7, C*H*$_2$CCH); 2.67–2.63 (*m*, C*H*$_2$CH=CH$_2$); 2.13 (*t*, *J* = 2.7, CH$_2$CC*H*); 1.62 (*s*, Me); 1.01 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 173.4 (*s*); 130.9 (*s*); 120.8 (*t*); 115.7 (*s*); 80.1 (*s*); 78.5 (*s*); 72.6 (*s*); 40.5 (*t*); 39.1 (*s*); 27.4 (*t*); 25.1 (*q*); 23.1 (*q*).

cis-**4**: ^{1}H-NMR (500 MHz): significant peaks 1.52 (*s*, Me); 1.03 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 130.9 (*s*); 41 (*s*); 27.2 (*s*).

7. *Ethyl 3-Ethenyl-2-hydroxypent-4-enoate* (**5**). A soln. of 5-bromopenta-1,3-diene (2.0 g, 13.6 mmol) in THF (5.0 ml) was added to a suspension of Zn (890 mg, 13.6 mmol) and AlCl$_3$ (1.8 g, 13.6 mmol) in THF (32.0 ml) at r.t. under N$_2$. After stirring for 15 min, a soln. of ethyl glyoxylate (1.38 g, 13.86 mmol) in THF (5.0 ml) was added, and the mixture was stirred for 8 h until all starting material was consumed. Then, the mixture was poured into sat. NH$_4$Cl soln. (10.0 ml) and extracted with Et$_2$O (3 × 40 ml). The combined org. phase was washed with brine, dried (MgSO$_4$), and evaporated, and the crude product was purified by FC (hexane/AcOEt 4:1): **5** (1.20 g, 52%). Pale yellow oil. IR (Film): 3501, 3080, 2982, 2937, 2936, 2935, 1737, 1639, 1371, 1255, 1250, 1109. 922. ^{1}H-NMR (360 MHz): 5.87–5.78 (*m*, 2 C*H*=CH$_2$); 5.18–5.11 (*m*, 2 CH=C*H*$_2$); 4.2 (*m*, C*H*OH, MeCH$_2$O); 3.18–3.17 (*m*, C*H*(CH=CH$_2$)$_2$); 2.85 (*d*, *J* = 6.1, OH); 1.27 (*t*, *J* = 5, *Me*CH$_2$O). ^{13}C-NMR (50.3 MHz): 173.424 (*s*); 136.48 (*s*); 134.7 (*s*); 117.76 (*s*); 116.91 (*s*); 73.54 (*s*); 61.59 (*s*); 51.92 (*s*); 14.2 (*s*). CI-MS: 171 (4, [*M* + 1]$^+$), 170 (36, *M*$^+$), 152 (11), 151 (5), 142 (3), 124 (14), 123 (8), 122 (5), 106 (10), 102 (6), 96 (35), 80 (12), 78 (30), 77 (7), 68 (27), 67 (54), 66 (100), 54 (24). Anal. calc. for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found: C 62.95, H 7.99.

8. *2-(*tert*-Butyl)-5-(1-ethenylprop-2-enyl)-1,3-dioxolan-4-one* (**6**). A mixture of **5** (2.0 g, 11.76 mmol), 2,2-dimethylpropanal (4.0 g, 94.08 mmol), TsOH (50 mg), and 1 drop of conc. H$_2$SO$_4$ soln. in pentane (20 ml) was heated under reflux with azeotropic removal of H$_2$O. After completion of the reaction (overnight), the soln. was washed with H$_2$O, dried (MgSO$_4$), and evaporated. The crude product was purified by FC (pentane/Et$_2$O 20:1): *cis*/*trans*-**6** 1:1 (1.60 g, 65%). IR (Film): 3583, 3084, 2976, 2910, 2876, 1799, 1485, 1363, 1201, 1103. CI-MS: 211 (42, [*M* + 1]$^+$), 194 (7), 193 (57), 189 (4), 183 (9), 175 (8), 171 (19), 167 (7), 166 (27), 152 (25), 147 (12), 142 (11), 137 (68), 126 (12), 124 (100), 114 (16). HR-MS: 211.13261 ($C_{12}H_{19}O_3^+$, [*M* + 1]$^+$; calc. 211.13286).

trans-**6**: ^{1}H-NMR (500 MHz): 5.97–5.83 (*m*, 2 C*H*=CH$_2$); 5.27–5.25 (*m*, H–C(2), 2 CH=C*H*$_2$); 4.45–4.44 (*dd*, *J* = 3.35, 1.6, H–C(5)); 3.31–3.25 (*m*, C*H*(CH=CH$_2$)$_2$); 0.94 (*s*, *t*-Bu). ^{13}C-NMR (126.76 MHz): 172 (*s*); 135.4 (*s*); 132.5 (*s*); 119.2 (*s*); 118.1 (*s*); 111.4 (*s*); 78.1 (*s*); 50.3 (*s*); 23.1 (*s*).

cis-**6**: ^{1}H-NMR (500 MHz): 5.99–5.82 (*m*, 2 C*H*=CH$_2$); 5.25–5.16 (*m*, 2 CH=C*H*$_2$); 5.1 (*d*, *J* = 1.3, H–C(2)); 4.36–4.34 (*dd*, *J* = 3.27, 1.37, H–C(5)); 3.36–3.32 (*m*, C*H*(CH=CH$_2$)$_2$); 0.98 (*s*, *t*-Bu). ^{13}C-NMR (126.76 MHz): 172 (*s*); 135.9 (*s*); 134.2 (*s*); 121 (*s*); 119 (*s*); 109.6 (*s*); 78.3 (*s*); 48.7 (*s*); 24 (*s*).

9. *2-(*tert*-Butyl)-5-(1-ethenylprop-2-enyl)-5-(prop-2-enyl)-1,3-dioxolan-4-one* (*cis*-**7**). According to *GP 1*, without HMPA, from *trans*-**6** (250 mg, 1.141 mmol), LDA (2.28 ml, 2.28 mmol), and 3-bromoprop-1-ene (552 mg, 6.45 mmol). FC (hexane/AcOEt 20:1) gave *cis*-**7** (155 mg, 53%) as a single diastereoisomer. IR (Film): 3583, 3082, 2978, 2963, 2936, 2910, 2876, 1796, 1484, 1409, 1365, 1198, 1152, 1085, 1045, 996, 973, 922. ^{1}H-NMR (500 MHz): 5.88–5.84 (*m*, 3 C*H*=CH$_2$); 5.2–5.13 (*m*, 3 CH=C*H*$_2$, H–C(2)); 3.19 (*m*, C*H*(CH=CH$_2$)$_2$); 2.64–2.59 (*ddt*, *J* = 14.18, 7.3, 1.2, 1 H, C*H*$_2$CH=CH$_2$); 2.54–2.49 (*ddt*, *J* = 12.99, 7.3, 1.2, 1 H, C*H*$_2$CH=CH$_2$); 1.0 (*s*, *t*-Bu). NOE (500 MHz): 5.16 (H–C(2)) → 2.64–2.49 (1.2%); 2.64–2.59 (C*H*$_2$CH=CH$_2$) → 5.16 (H–C(2), 2.7%); 2.54–2.49 (C*H*$_2$CH=CH$_2$) → 5.16 (H–C(2), 2.6%); 1.0 (*t*, Bu) → 3.1

(C*H*(CH=CH_2)$_2$), 0.1%), 5.8 (CH(C*H*=CH_2)$_2$), 0.6%). ^{13}C-NMR (125.7 MHz): 173 (*s*); 135.4 (*s*); 134.5 (*s*); 131.1 (*s*); 120.8 (*s*); 119.5 (*s*); 118.6 (*s*); 108.9 (*s*); 84 (*s*); 53.5 (*s*); 38.4 (*s*); 34.5 (*s*); 24.5 (*s*). CI-MS: 251 (9, [*M* + 1]$^+$), 239 (9), 233 (3), 205 (9), 180.9 (6), 164 (11), 154 (14), 152 (2), 146 (3), 137 (8), 136 (100), 120 (6), 118 (10). 114 (39), 94 (10), 80 (10), 68 (5), 66 (7). Anal. calc. for $C_{15}H_{22}O_3$ (250.34): C 71.97, H 8.86; found: C 71.93, H 8.94.

10. *2-(*tert*-Butyl)-2-methyl-1,3-dioxaspiro[4.5]dec-7-en-4-one* (**9**). To a soln. of *cis*/*trans*-**3** 2:1 (225 mg, 0.90 mmol) in dry benzene (10.0 ml), **8** (2 mol-%, 15.0 mg, 0.02 mmol) was added at r.t. and stirred overnight. After evaporation, the crude product was purified by FC (AcOEt/hexane 1:10): *cis*/*trans*-**9** 2:1 (200 mg, 98%). IR (Film): 2976, 2967, 2933, 1790, 1485, 1379, 1286, 1265, 1153, 1089, 1028, 929. CI-MS: 225 (100, *M*$^+$), 199 (12), 167 (50), 139 (38), 125 (31), 101 (53), 97 (83), 79 (48), 57 (63). Anal. calc. for $C_{13}H_{20}O_3$ (224.303): C 69.61, H 8.99; found: C 69.47, H 9.04.

cis-**9**: ^{1}H-NMR (500 MHz): 5.86–5.82 (*m*, C*H*=CH); 5.66–5.62 (*m*, CH=C*H*); 2.59–2.57 (*m*, 1 H); 2.33–2.21 (*m*, 3 H); 1.93–1.89 (*m*, 2 H); 1.56 (*s*, Me); 1.03 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 175.8 (*s*); 127.3 (*d*); 122.5 (*d*); 115.3 (*s*); 38.9 (*s*); 35.4 (*t*); 29.8 (*t*); 25.0 (*q*); 23.4 (*q*); 21.6 (*t*).

trans-**9**: ^{1}H-NMR (500 MHz); 5.84–5.75 (*m*, C*H*=CH); 5.64–5.60 (*m*, CH=C*H*); 2.61–2.50 (*m*, 1 H); 2.32–2.18 (*m*, 3 H); 1.98–1.87 (*m*, 2 H); 1.55 (*s*, Me); 1.00 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 175.7 (*s*); 126.7 (*d*); 123.0 (*d*); 114.9 (*s*); 39.1 (*s*); 34.0 (*t*); 31.2 (*t*); 25.0 (*q*); 23.4 (*q*); 21.7 (*t*).

11. *2-(*tert*-Butyl)-7-ethenyl-2-methyl-1,3-dioxaspiro[4.4]non-7-en-4-one* (*trans*-**10**). To a soln. of *trans*/*cis*-**4** 2.5:1 (101 mg, 0.45 mmol) in dry CH_2Cl_2 (4.0 ml), **8** (10 mol-%, 37.0 mg, 0.045 mmol) was added at r.t. The soln. was heated under reflux for 8 days. After evaporation, the crude product was purified by FC (AcOEt/hexane 1:10): *trans*-**10** (80 mg, 65%) as a single diastereoisomer. IR (Film): 2976, 2967, 2933, 1790, 1485, 1379, 1286, 1265, 1153, 1089, 1028, 929. ^{1}H-NMR (500 MHz): 6.50 (*dd*, *J* = 10.6, 17.4, CH=C–C*H*=CH_2); 5.67–5.66 (*m*, C*H*=C–CH=CH_2); 5.12 (*d*, *J* = 10.6, 1 H, CH=CH_2); 5.05 (*d*, *J* = 17.4, 1 H, CH=CH_2); 3.13–3.07 (*m*, 2 H); 2.84–2.80 (*m*, 2 H); 1.55 (*s*, Me); 1.00 (*s*, *t*-Bu). ^{13}C-NMR (125.76 MHz): 176.8 (*s*); 139.6 (*s*); 132.7 (*d*); 126.8 (*d*); 119.6 (*s*); 115.5 (*t*); 84.5 (*s*); 45.7 (*t*); 45.3 (*t*); 38.8 (*s*); 24.8 (*q*); 22.5 (*q*). CI-MS: 237 (2, *M*$^+$), 179 (8), 165 (11), 151 (13), 137 (100), 119 (19), 101 (71), 91 (9), 79 (9), 57 (13). Anal. calc. for $C_{14}H_{20}O_3$ (236.314): C 71.16, H 8.53; found: C 71.45, H 8.55.

12. *2-(*tert*-Butyl)-6-ethenyl-1,3-dioxaspiro[4.4]non-7-en-4-one* (**11**). A soln. of **7** (130 mg, 0.52 mmol) and **8** (3 mol-%, 5.0 mg, 0.018 mmol) in dry CH_2Cl_2 (7.5 ml) was stirred at r.t. for 6 h. The solvent was evaporated, and the crude product was purified by FC (hexane/AcOEt 20:1): **11** (100 mg, 87%) as a non-separable 66:34 mixture of diastereoisomers. IR (Film): 3565, 3510, 3474, 3453, 3438, 3427, 3414, 3405, 3395, 3384, 3376, 3362, 3341, 3253, 2965, 2940, 2910, 2877, 1793, 1733, 1484, 1465, 1409. ^{1}H-NMR (500 MHz): 5.90–5.65 (*m*, C*H*=CH_2, C*H*=C*H*); 5.20–5.11 (*m*, CH=CH_2, H–C(2)); 3.8 (*m*, C*H*CH=CH_2, maj.); 3.65 (*m*, C*H*CH=CH_2, min.); 2.92 (*m*, 1 H, CH_2CH=CH); 2.88 (*m*, 1 H, CH_2CH=CH); 1.0 (*s*, *t*-Bu). ^{13}C-NMR (125.7 MHz): 176.1 (*s*, min.); 174.0 (*s*, maj.); 135.0 (*s*, min.); 134.5 (*s*, maj.); 132.3 (*s*, maj.); 131.8 (*s*, min.); 127.5 (*s*, min.); 127.1 (*s*, maj.); 117.8 (*d*); 108.7 (*d*); 87.6 (*s*, maj.); 86.7 (*s*, min.); 60.1 (*s*, min.); 57.1 (*s*, maj.); 42.4 (*s*, min.); 41.9 (*s*, maj.); 34.8 (*s*, maj.); 34.6 (*s*, min.); 24.0 (*s*, maj.); 23.8 (*s*, min.). CI-MS: 223 (28, [*M* + 1]$^+$), 222 (6, *M*$^+$), 205 (15), 186 (21), 178 (9), 176 (5), 164 (26), 158 (4), 152 (6), 148 (10), 137 (9), 136 (100), 135 (11), 134 (4), 120 (14), 118 (29), 114 (10), 108 (30), 107 (20), 92 (40), 86 (28), 80 (32), 79 (81), 78 (9). Anal. calc. for $C_{13}H_{18}O_3$ (222.28): C 70.24, H 8.16; found: C 70.20, H 8.18.

13. *Synthesis of (–)-Quinic acid. (2*R*,5*S*)-5-(But-3-enyl)-2-(*tert*-butyl)-2-methyl-5-(prop-2-enyl)-1,3-dioxolan-4-one* ((2*R*,5*S*)-**3**). According to *GP 1*, from (*R*)-**1** (800 mg, 5.1 mmol; 80% ee), LDA (10.2 ml, 10.2 mmol), and 4-iodobut-1-ene (3.8 mg, 20.4 mmol). FC (Et$_2$O/hexane 1:20) gave (2*R*)-**2** (730 mg, 67%) as a *trans*/*cis* 3:1 diastereoisomer mixture. To this diastereoisomer mixture (993 g, 4.7 mmol) in THF (3.0 ml) at –78°, 0.5M KHMDS in toluene (19.0 ml, 9.5 mmol) was added slowly. After 30 min, a soln. of 3-bromoprop-1-ene (1.20 ml, 14.1 mmol) in THF (3.0 ml) was added. The resultant mixture was allowed to warm to r.t. overnight, then treated with sat. $NaHCO_3$ soln. (10.0 ml), and extracted with Et$_2$O (3 × 30 ml). The combined org. phase was washed with sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the crude product was purified by FC (Et$_2$O/hexane 1:20): **3** (950 mg, 80%) as a *cis*/*trans* 2:1 diastereoisomer mixture. Separation of the diastereoisomers was performed by LP-FC (Et$_2$O/hexane 1:40): (2*R*,5*S*)-**3** in 51% yield. $[\alpha]_D^{20} = -16.3$ (*c* = 1.13, CH_2Cl_2). IR, NMR, and CI-MS: identical with those of (±)-*trans*-**3**.

*(2*R*,5*S*)-2-(*tert*-Butyl)-2-methyl-1,3-dioxaspiro[4.5]dec-7-en-4-one* ((2*R*,5*S*)-**9**). As described for racemic **9** (see above), from (2*R*,5*S*)-**3** (195 mg, 0.77 mmol) in dry benzene (5.0 ml) and **8** (2 mol-%, 13.0 mg, 0.02 mmol). FC (AcOEt/hexane 1:20) gave (2*R*,5*S*)-**9** (162 mg, 94%). $[\alpha]_D^{20} = -14.05$ (*c* = 1.31, CH_2Cl_2). IR, NMR, and CI-MS: identical with those of (±)-*trans*-**9**.

*Methyl (*S*)-1-Hydroxycyclohex-3-enecarboxylate* ((*S*)-**12**). Anh. HCl was bubbled through a soln. of (2*R*,5*S*)-**9** (136 mg, 0.61 mmol) in abs. MeOH (5.0 ml) for 2 min, and the soln. was heated under reflux

overnight. After cooling to r.t., solid $NaHCO_3$ was added, and the heterogeneous soln. was stirred for 10 min. The solvent was evaporated, and the residue was dissolved in H_2O (10 ml). The aq. phase was extracted with CH_2Cl_2 (3×20 ml), the combined org. phase was washed with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated, and the crude product was purified by FC (AcOEt/hexane 1:10): (*S*)-**12** (94 mg, 98%). Colorless oil. $[\alpha]_D^{20} = +20.11$ ($c = 0.92$, CH_2Cl_2) and 80% ee (GC, 80°). ^{1}H-NMR (500 MHz): 5.80–5.77 (*m*, C*H*=CH); 5.67–5.62 (*m*, CH=C*H*); 3.79 (*s*, CO_2Me); 3.0 (*s*, OH); 2.63–2.57 (*m*, 1 H, CH_2CH$_2$); 2.36–2.27 (*m*, 1 H, CH_2CH$_2$); 2.15–2.07 (*m*, CH_2CH=CH); 1.97–1.91 (*m*, 1 H, CH$_2$CH_2CH=CH); 1.8–1.76 (*m*, 1 H, CH$_2$CH_2CH=CH). ^{13}C-NMR (125.76 MHz): 177.6 (*s*); 126.7 (*d*); 123.1 (*d*); 72.7 (*s*); 53.1 (*q*); 35.3 (*t*); 31.0 (*t*); 21.7 (*t*). IR (Film): 3497 (br., OH), 2980, 2931, 1728, 1447, 1255, 1221, 1095, 1043. CI-MS: 157 (72, $[M+1]^+$), 139 (100), 125 (9), 107 (9), 97 (43), 79 (93), 67 (4), 54 (4). Anal. calc. for $C_8H_{12}O_3$ (156.183): C 61.52, H 7.74; found: C 61.28, H 7.73.

4-Bromo-1-hydroxy-6-oxabicyclo[3.2.1]octan-7-one (**13**). To a soln. of (*S*)-**12** (120 mg, 0.76 mmol) in MeOH (6.0 ml), 1M NaOH (1.0 ml, 0.91 mmol) was added at r.t. and stirred for 3 h. After evaporation, the white residue was dissolved in H_2O (4.0 ml), and Br_2 (0.08 ml, 1.52 mmol) was added. After 3 h at r.t., the mixture was extracted with CH_2Cl_2 (3×15 ml), the combined org. phase was washed with sat. Na_2SO_3 soln. and brine, dried ($MgSO_4$), and evaporated, and the crude product was purified by FC (AcOEt/hexane 1:5): **13** (120 mg, 65%). Pale yellow oil. $[\alpha]_D^{20} = -9.12$ ($c = 1.36$, CH_2Cl_2) and 82% ee (GC, 180°). ^{1}H-NMR (500 MHz): 4.84 (*ddd*, $J =$ 0.84, 4.21, 6.2, CHO); 4.34 (*t*, $J = 4.7$, CHBr); 2.98 (*s*, OH); 2.84 (*d*, $J = 11.9$, 1 H–C(8)); 2.48 (*dd*, $J = 6.2$, 11.8, 1 H–C(8)); 2.40–2.13 (*m*, 3 H, CH_2CH_2CHBr); 1.83–1.79 (*m*, 1 H, CH_2CH$_2$CHBr). ^{13}C-NMR (125.76 MHz): 178.0 (*s*); 77.8 (*d*); 43.5 (*d*); 38.9 (*t*); 28.7 (*t*). Spectral data in accordance with [13c].

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