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Titanocene-promoted stereoselective eliminations on epoxy alcohols derived from R-(−)-carvone

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ABSTRACT

The reaction of several stereoisomeric epoxy alcohols, obtained from R-(−)-carvone, and their corresponding formates, acetates, and benzoates, promoted by Cp_2TiCl has been studied. The different outcomes of the reaction of epoxy derivatives are rationalized in terms of mechanistically biased processes. The radicals emerging from oxirane cleavage provide two types of reaction: dehydroxylation (deoxycarbonylation) and dehydrogenation.

The results offer considerable support for the radical elimination theory of hydroxyl, formyloxyl, and acetoxyl groups. The inability of tertiary radicals to be reduced by the Ti(III) complex is demonstrated unequivocally.

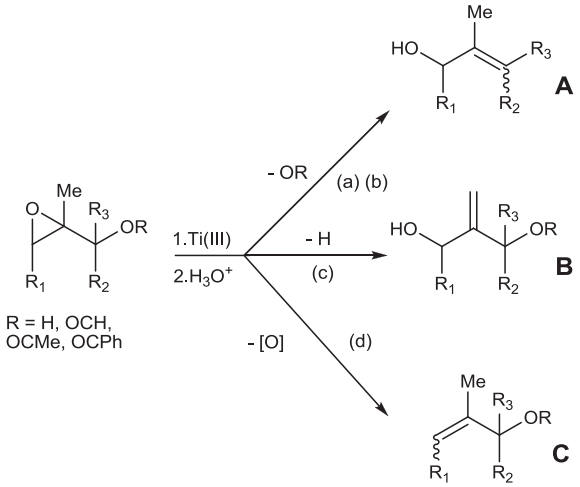
1. Introduction

In a previous paper[1] we studied the reaction of a series of noncyclic 2,3-epoxy alcohols and their corresponding formates, acetates, and benzoates, promoted by Cp_2TiCl. The different outcomes of the reaction of epoxy derivatives were rationalized in terms of mechanistically biased processes. After homolytic oxirane cleavage, four main types of reaction were found: (a) dehydroxylation[2] (for alcohols), (b) deoxycarbonylation (for esters)[3] (c) dehydrogenation,[4] and (d) deoxygenation.[5] The reaction products varied according to the substitution pattern. The radical nature of these eliminations was demonstrated using a kinetic method (see Scheme 1).[3b]

In that paper[1] we found that the primary alcohol trisubstituted epoxide system (R=H, R_1=*n*-Hex, R_2=R_3=H) and its formate (R=HC=O) led exclusively to hydroxyl and formyloxyl elimination, to afford the allylic alcohol **A** in 85% and 83% yield, respectively. The corresponding primary epoxy acetate (R=Me–C=O) and epoxy benzoate (R=Ph–C=O) mainly afforded the elimination of hydrogen to give the allylic alcohol **B**, in 64% and 73% yield, respectively.[1]

While the secondary alcohol trisubstituted epoxide system (R=R_1=R_3=H, R_2=*n*-Hex) gave a mixture of dehydroxylation **A** (34%) dehydrogenation **B** (23%) and deoxygenation **C** (27%) products, its formate (R=HC=O) only gave the deoxycarbonylation product **A** (88%). The corresponding secondary epoxy acetate (R=Me–C=O) afforded a mixture of deoxycarbonylation **A** (66%) and dehydrogenation **B** (17%) and the epoxy benzoate (R=Ph–C=O) gave a mixture of **A** (45%) and **B** (50%).[1]

The tertiary alcohol trisubstituted epoxide system (R=R_1=H, R_3=R_2=*n*-Bu) afforded deoxygenation product **C** (53%) as the major product, but dehydrogenation **B** (4%) and dehydroxylation **A** (27%)



Scheme 1. Elimination reactions induced by titanocene on epoxy alcohols and epoxyesters.

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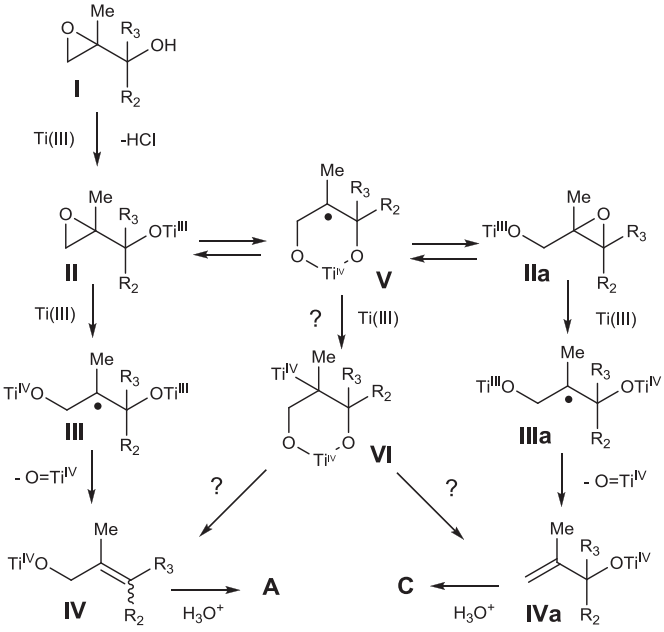
products were also obtained. These experimental data show that elimination of the hydroxy groups is faster for primary alcohols. Among the esters, the formyloxyl was the fastest leaving group. The acetate and benzoate of the secondary alcohols were eliminated faster than the primary ones.[1]

2. Results and discussion

In all these reactions the main intermediate is a tertiary radical that arises from the regioselective homolytic rupture of the oxirane, promoted by Ti (III). If as has been stated, the tertiary radicals are not reduced with Ti(III), due to steric hindrance,[1–6] deoxygenation product **C** from secondary alcohol trisubstituted epoxide systems **I** (R_2=*n*-Hex, R_3=H), and tertiary alcohol trisubstituted epoxide system **I** (R_2=R_3=*n*-Bu)[1] should not have been formed. To explain this, we suggest that the deoxygenation process that leads to **C** could occur in terms of an equilibrium between the intermediate **II** and the regioisomer **IIa** through a six-membered Ti^{IV} intermediate **V**. The equilibrium should clearly be displaced to the right for the tertiary epoxy-alcohol[1] (Scheme 2).



Scheme 2. Equilibration of intermediates.

To check the above hypothesis and to observe the influence of the spatial orientation of both the epoxydes as the leaving groups, in the removal rate, we chose some derivatives of cyclohexane with a rigid conformation, in which the functional groups involved in the reaction were substituents with varying orientations (see Fig. 1).

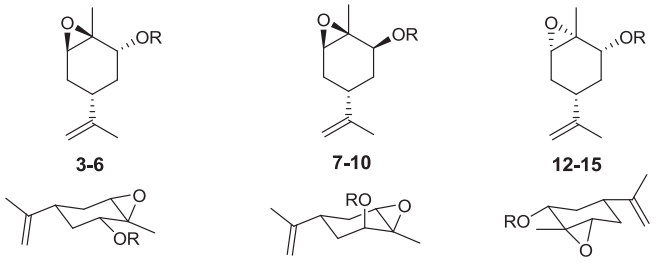
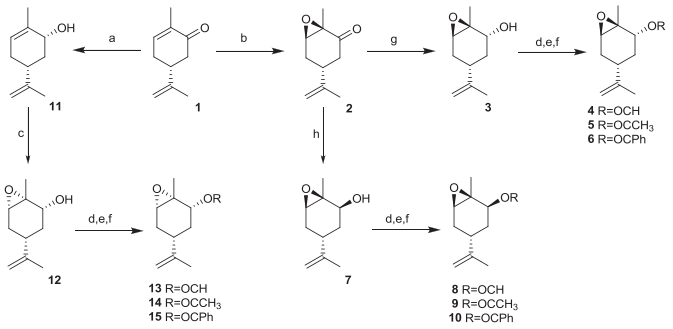


Fig. 1. Cyclohexane derivatives with a rigid conformation.

All three epoxy alcohol isomers were prepared from *R*-(−)-carvone **1**, following the procedure described by S. Kirsch and T. Bach.[7] The corresponding esters (formates, acetates, benzoates) were obtained by standard procedures (see Scheme 3).



Scheme 3. Synthesis of epoxy alcohols **3**, **7**, and **12**, and their ester derivatives. (a) $NaBH_4$, $CeCl_3$, MeOH, 75%; (b) H_2O_2, NaOH, MeOH, 92%; (c) *m*CPBA, CH_2Cl_2, 88%; (d) FAM; (e) Ac_2O, DMAP, pyr; (f) PhCOCl; (g) $NaBH_4$, $CeCl_3$, MeOH, 91%; (h) L-Selectride, THF, 94%.

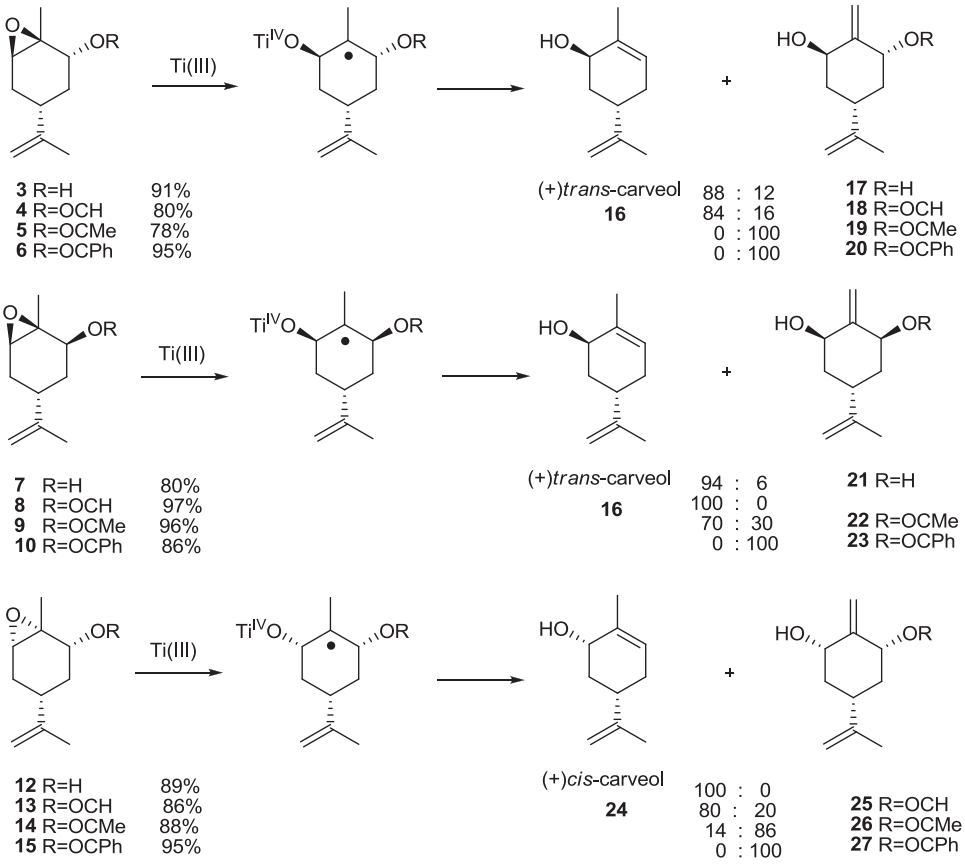
2.1. Radical reactions induced by titanocene chloride

The reaction of these epoxyderivatives with titanocene chloride was carried out by adding a substrate solution in tetrahydrofuran to another of Ti (III) in the same solvent at room temperature.[1] The extraction and isolation of the reaction products were performed by the usual procedures. The only reaction products obtained were those resulting from the β-elimination of OR and/or hydrogen. In no case, oxirane deoxygenation products were obtained. The results are quoted in Scheme 4.

The data in Scheme 4 show that the predominant reaction with epoxy alcohols and epoxy formates was in all cases dehydroxylation or deformylation, whatever the orientation, axial/equatorial, of the leaving group. The major product in these cases was **16** (+)-*trans*-carveol[8] or **24** (+)-*cis*-carveol.[9] For epoxyacetates, dehydrogenation predominated, except for **9**, which gives **16** (+)-*trans*-carveol as the major product, resulting from the deacetoxylation.[10] The difference in reactivity of **9**, can be attributed to the axial orientation of the acetoxy group in the transition state; in the other acetates the orientation was equatorial. For epoxy benzoates, the main reaction was the dehydrogenation. Debenzoyloxylation did not occur.

Tables 1 and 2 show the optical rotation of compounds **16**, (+)-*trans*-carveol, and **24**, (+)-*cis*-carveol, depending on which epoxy derivative they came from.

The results shown in Scheme 4 lend considerable support to the radical elimination theory of hydroxyl, formyloxyl, acetoxyl and benzoyloxyl groups, which we have reported previously.[1] They also add further to the already numerous examples that illustrate the inability of the complex of Ti (III) to reduce tertiary radicals. In the hypothetical case that this reduction takes place with the radical intermediates **3A**, **7A**, **12A**, resulting from the opening of the epoxy alcohols **3**, **7**, **12**, the C–Ti(IV) complexes **3B**, **7B**, **12B**, represented in Scheme 5 would be obtained. The major products of the evolution of such intermediates would correspond to the oxirane deoxygenation product,[1,4] which would afford (−)-*cis*-carveol, (−)-*trans*-carveol and (−)-*cis*-carveol from **3**, **7**, and **12**, respectively. This result is the inverse of those obtained experimentally. The reaction of epoxy alcohols **7** and **12** with Ti (III) should not evolve through the bicyclic intermediates **7C** and **12C**, similar to intermediate **V** in Scheme 2, since in that case mixtures of carveols (racemic) would be obtained, as shown in Scheme 6.



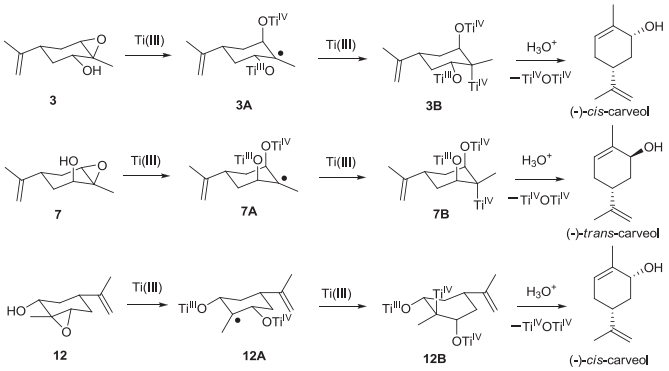
Scheme 4. Elimination reaction on epoxy alcohols and epoxyesters.

Table 1
Optical rotation of (+)-*trans*-carveol

Entry	From	**16** $[\alpha]_D^{20}$
1	**3**	+151.5
2	**4**	+143.8
3	**7**	+114.0
4	**8**	+139.6
5	**9**	+129.3

Table 2
Optical rotation of (+)-*cis*-carveol

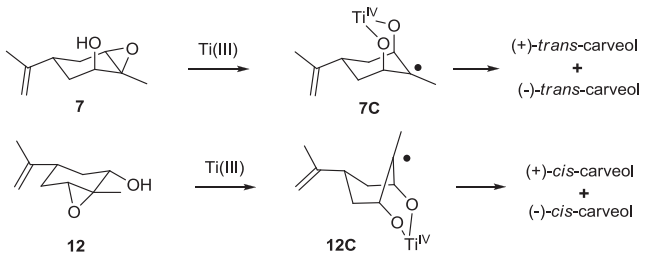
Entry	From	**24** $[\alpha]_D^{20}$
1	**12**	+30.6
2	**13**	+16.1
3	**14**	+17.6



Scheme 5. Evolution of hypothetical intermediates.

3. Conclusion

In sum, we have demonstrated that the reaction of several stereoisomeric epoxy alcohols, obtained from *R*-(−)-carvone and their corresponding formates, acetates, and benzoates, promoted by Cp_2TiCl, evolves in two ways through the radical arising from oxirane cleavage: dehydroxylation (decarboxylation) and dehydrogenation. The different outcomes of the reaction of epoxy derivatives are rationalized in terms of mechanistically biased processes. The epoxy alcohols **3** and **7** mainly produced (+)-*trans*-carveol and **12** gave (+)-*cis*-carveol. In a similar way, the epoxy



Scheme 6. Evolution of hypothetical intermediates.

formates **4** and **8** mainly afforded (+)-*trans*-carveol and **13** afforded (+)-*cis*-carveol. Radical elimination of the acetoxyl group only occurred predominantly for the epoxy acetate **9**, due to its original axial orientation. These results mean that elimination of hydroxyl, formyloxyl, and acetoxyl groups could only occur in a radical way in the form OTi^{IV}, or $ROCOTi^{IV}$. Benzoyloxyl elimination was not observed with any of the epoxy benzoates tested. All these results strongly support the radical elimination theory, of hydroxyl, formyloxyl, and acetoxyl groups. The inability of tertiary radicals to be reduced by the Ti(III) complex is demonstrated unequivocally.

4. Experimental section

R-(−)-Carvone was purchased, $[\alpha]_D^{20}$ −55.6 ($CHCl_3$, *c* 40 mg/mL), from Aldrich Chemical Company, Inc.

4.1. General methods

Melting points are uncorrected. ^1H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^1H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise stated. Standard mass spectrometry data were acquired using a GC–MS system in EI mode with a maximum *m*/*z* range of 600. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash-column techniques on Merck silica gel 60 (0.040–0.063 mm). The yields reported are for chromatographically pure isolated products unless otherwise stated.

4.2. General procedure 1 (GP1)

4.2.1. Reaction of epoxides with Cp_2TiCl. A mixture of Cp_2TiCl_2 (2.20 mmol) and Zn (6.60 equiv) in strictly deoxygenated THF (10 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) was dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added via cannula to the epoxide solution. After 30 min, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

4.3. Reaction of (1*S*,2*R*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol 3 with Cp_2TiCl

According to GP1, reaction of **3** (100 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane/EtAcO 7:3) furnished (1*R*,5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **16** (78 mg, 79%) and (1*R*,3*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexane-1,3-diol **17** (12 mg, 12%).

Data for **16**: IR, ν=3325, 3078, 2923, 1645, 1443, 1378, 1171, 1061 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.57 (dt, J_1=4.0 Hz, J_1=13.2 Hz, 1H), 1.7–2.4 (m, 4H), 1.73 (s, 3H), 1.78 (s, 3H), 3.99 (br s, 1H), 4.70 (s, 2H), 5.55 (d, *J*=5.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.6 ($2CH_3$), 30.8 (CH_2), 35.0 (CH), 36.7 (CH_2), 68.1 (CH), 108.7 (CH_2), 124.9 (CH), 134.3 (C), 149.0 (C) ppm; MS EI, *m*/*z* (relative intensity): 134 (M^+−18, 5), 119 (11), 99 (2), 94 (12), 86 (18), 71 (100), 55 (20); HRMS (ESI): calcd for $C_{10}H_{16}ONa$ 175.1099; found 175.1101. $[\alpha]_D^{20}$ 151.5 ($CHCl_3$, *c* 4 mg/mL).

Data for **17**: IR, ν=3354, 2914, 1432, 1368, 1167, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.73 (s, 3H), 1.2–2.7 (m, 5H), 4.00 (br s, 1H), 4.56 (br s, 1H), 4.72 (br s, 2H), 5.01 (br s, 1H), 5.10 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.8 (CH_3), 37.5 (CH), 38.6 (CH_2), 41.9 (CH_2), 68.7 (CH), 73.4 (CH), 107.4 (CH_2), 109.3 (CH_2), 148.1 (C), 152.1 (C) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−18, 3), 132 (21), 94 (12), 86 (34), 71 (85), 55 (100); HRMS (ESI): calcd for $C_{10}H_{16}O_2Na$ 191.1048; found 191.1449.

4.4. Reaction of (1*S*,2*R*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl formate 4 with Cp_2TiCl

According to GP1, reaction of **4** (100 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane 8:2 AcOEt) furnished **16** (57 mg, 67%) and **18** (14 mg, 14%).

Data for **16**: $[\alpha]_D^{20}$ 143.8 ($CHCl_3$, *c* 12 mg/mL).

Data for **18**: IR, ν=2977, 2923, 1723, 1168 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.0–2.7 (m, 5H), 1.72 (s, 3H), 4.05 (br s, 1H), 4.73 (m, 4H), 5.03 (m, 1H), 8.09 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.7 (CH_3), 36.6 (CH_2), 38.0 (CH_2), 40.7 (CH), 71.4 (CH), 74.1 (CH), 108.0 (CH_2), 109.2 (CH_2), 148.0 (2C), 160.7 (CH) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−46, 3), 132 (11), 121 (51), 94 (32), 86 (38), 67 (100), 55 (52); HRMS (ESI): calcd for $C_{11}H_{16}O_3Na$ 219.0992; found 219.0993.

4.5. Reaction of (1*S*,2*R*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl acetate 5 with Cp_2TiCl

According to GP1, reaction of **5** (100 mg, 0.5 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7:3 diethyl ether) furnished **19** (67 mg, 85%): IR, ν=2947, 1738, 1459, 1370, 1252, 1030, 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.71 (s, 3H), 1.2–2.8 (m, 5H), 2.12 (s, 3H), 4.53 (s, 1H), 4.71 (br s, 1H), 4.88 (s, 2H), 4.96 (s, 1H), 5.63 (dd, J_1=5.1 Hz, J_2=11.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.7 (CH_3), 21.0 (CH_3), 37.2 (CH), 38.3 (CH_2), 38.5 (CH_2), 71.0 (CH), 73.2 (CH), 107.5 (CH_2), 109.5 (CH_2), 147.8 (2C), 170.1 (C) ppm; MS EI, *m*/*z* (relative intensity): 168 (M^+−42, 2), 150 (10), 135 (8), 121 (31), 106 (10), 92 (37), 81 (45), 71 (100), 58 (91); HRMS (ESI): calcd for $C_{12}H_{18}O_3Na$ 233.1148; found 233.1150. $[\alpha]_D^{20}$ −80.9 ($CHCl_3$, *c* 2 mg/mL).

4.6. Reaction of (1*S*,2*R*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl benzoate 6 with Cp_2TiCl

According to GP1, reaction of **6** (100 mg, 0.4 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7:3 diethyl ether) furnished **20** (95 mg, 95%): IR, ν=2917, 2665, 1697, 1430, 1295, 1113, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.76 (s, 3H), 1.2–2.3 (m, 5H), 4.13 (br s, 1H), 4.76 (m, 4H), 5.20 (dt, J_1=4.4 Hz, J_2=10.8 Hz, 1H), 7.2–7.5 (m, 3H), 8.0–8.2 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.9 (CH_3), 36.9 (CH), 38.0 (CH_2), 38.4 (CH_2), 71.8 (CH), 73.3 (CH), 108.0 (CH_2), 109.2 (CH_2), 128.5 (2CH), 129.5 (CH), 130.2 (2CH), 133.7 (C), 147.6 (C), 148.3 (C), 171.9 (C) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−122, 3), 135 (2), 122 (1), 117 (6), 105 (100), 91 (4), 77 (28), 51 (11); HRMS (ESI): calcd for $C_{17}H_{20}O_3Na$ 295.1305; found 295.1311.

4.7. Reaction of (1*S*,2*S*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol 7 with Cp_2TiCl

According to GP1, reaction of **7** (100 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7:3 AcOEt) furnished (1*R*,5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **16** (68 mg,

75%), $[\alpha]_D^{20}$ 114 ($CHCl_3$, *c* 4 mg/mL) and (1*R*,3*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexane-1,3-diol **21** (5 mg, 5%).

Data for **21**: IR, ν=3353, 2912, 1430, 1362, 1169, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.73 (s, 3H), 1.2–2.7 (m, 5H), 4.56 (m, 2H), 4.73 (br s, 2H), 5.02 (s, 1H), 5.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.8 (CH_3), 37.5 (CH), 38.6 (CH_2), 42.0 (CH_2), 68.8 (CH), 73.4 (CH), 107.5 (CH_2), 109.3 (CH_2), 148.1 (C), 152.2 (C) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−18, 2), 132 (23), 94 (15), 86 (24), 71 (65), 55 (100); HRMS (ESI): calcd for $C_{10}H_{16}O_2Na$ 191.1048; found 191.1450.

4.8. Reaction of (1*S*,2*S*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl formate 8 with Cp_2TiCl

According to GP1, reaction of **8** (125 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane/EtAcO 8:2) furnished **16** (98 mg, 97%), $[\alpha]_D^{20}$ 139.6 ($CHCl_3$, *c* 5 mg/mL).

4.9. Reaction of (1*S*,2*S*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl acetate 9 with Cp_2TiCl

According to GP1, reaction of **9** (100 mg, 0.5 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished **16** (48 mg, 66%), $[\alpha]_D^{20}$ 129.3 ($CHCl_3$, *c* 23 mg/mL) and **22** (30 mg, 30%).

Data for **22**: IR, ν=2947, 1738, 1456, 1368, 1241, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.73 (s, 3H), 1.2–2.1 (m, 5H), 2.05 (s, 3H), 4.38 (m, 1H), 4.79 (br s, 1H), 4.80 (br s, 2H), 5.19 (br s, 2H), 5.53 (t, *J*=3.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.0 (CH_3), 21.4 (CH_3), 32.9 (CH), 36.2 (CH_2), 38.9 (CH_2), 71.7 (CH), 74.0 (CH), 109.8 (CH_2), 116.5 (CH_2), 144.5 (C), 147.7 (C), 169.6 (C) ppm; MS EI, *m*/*z* (relative intensity): 168 (M^+−42, 3), 150 (8), 135 (12), 121 (27), 106 (13), 92 (27), 81 (47), 71 (98), 58 (100); HRMS (ESI): calcd for $C_{12}H_{18}O_3Na$ 233.1148; found 233.1149.

4.10. Reaction of (1*S*,2*S*,4*S*,6*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl benzoate 10 with Cp_2TiCl

According to GP1, reaction of **10** (100 mg, 0.4 mmol) with Cp_2TiCl followed by flash chromatography (hexane 6:4 diethyl ether) furnished **23** (86 mg, 86%): IR, ν=2910, 2664, 1694, 1424, 1298, 1115, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.81 (s, 3H), 1.5–2.6 (m, 5H), 4.05 (s, 1H), 4.76 (m, 4H), 5.60 (m, 1H), 7.3–7.6 (m, 3H), 8.0–8.2 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.7 (CH_3), 30.9 (CH_2), 35.1 (CH), 36.6 (CH_2), 68.6 (CH), 71.2 (CH), 108.9 (CH_2), 109.4 (CH_2), 128.4 (2CH), 128.6 (C), 129.3 (C), 130.1 (2CH), 133.6 (CH+C), 171.9 (C) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−122, 8), 134 (42), 122 (1), 119 (29), 105 (100), 77 (67), 55 (28); HRMS (ESI): calcd for $C_{17}H_{20}O_3Na$ 295.1305; found 295.1309.

4.11. Reaction of (1*R*,2*R*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol 12 with Cp_2TiCl

According to GP1, reaction of **12** (100 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane/EtAcO 7:3) furnished (1*S*,5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **24** (87 mg, 89%): IR, ν=3322, 3072, 2921, 1443, 1372, 1176, 1054 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.2–2.3 (m, 5H), 1.73 (br s, 6H), 4.21 (br s, 1H), 4.73 (s, 2H), 5.50 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.2 (CH_3), 20.8 (CH_3), 31.2 (CH_2), 38.1 (CH_2), 40.6 (CH), 71.1 (CH), 109.3 (CH_2), 124.1 (CH), 136.5 (C), 149.2 (C) ppm; $[\alpha]_D^{20}$ 30.6 ($CHCl_3$, *c* 14 mg/mL).

4.12. Reaction of (1*R*,2*R*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl formate 13 with Cp_2TiCl

According to GP1, reaction of **13** (125 mg, 0.6 mmol) with Cp_2TiCl followed by flash chromatography (hexane/EtAcO 8:2) furnished **24** (53 mg, 68%), $[\alpha]_D^{20}$ 16.1 ($CHCl_3$, *c* 18 mg/mL) and **25** (18 mg, 18%).

Data for **25**: IR, ν=3420, 2929, 1720, 1462, 1191 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.9–2.2 (m, 5H), 1.72 (s, 3H), 4.11 (m, 1H), 4.77 (m, 2H), 4.85 (m, 1H), 5.01 (s, 1H), 5.14 (s, 1H), 8.16 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.9 (CH_3), 26.1 (CH_2), 32.0 (CH_2), 39.4 (CH), 70.7 (CH), 73.9 (CH), 109.5 (CH_2), 110.4 (CH_2), 147.5 (C), 148.5 (CH), 160.5 (CH) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−46, 2), 132 (3), 121 (34), 94 (14), 86 (58), 67 (97), 55 (100); HRMS (ESI): calcd for $C_{11}H_{16}O_3Na$ 219.0991; found 219.0992.

4.13. Reaction of (1*R*,2*R*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl acetate 14 with Cp_2TiCl

According to GP1, reaction of **14** (100 mg, 0.5 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished **24** (9 mg, 12%, $[\alpha]_D^{20}$ 17.6 ($CHCl_3$, *c* 4 mg/mL)) and **26** (76 mg, 76%).

Data for **26**: IR, ν=2947, 1734, 1451, 1369, 1248, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.71 (s, 3H), 1.2–2.2 (m, 5H), 2.13 (s, 3H), 4.15 (m, 1H), 4.73 (m, 2H), 4.95 (s, 1H), 5.10 (s, 1H), 5.20 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.5 (CH_3), 20.9 (CH_3), 37.9 (CH_2), 39.2 (CH), 41.2 (CH_2), 70.5 (CH), 71.9 (CH), 101.7 (CH_2), 109.9 (CH_2), 146.8 (C), 149.2 (C), 169.9 (C) ppm; MS EI, *m*/*z* (relative intensity): 168 (M^+−42, 2), 150 (8), 135 (18), 121 (26), 106 (5), 92 (34), 81 (41), 71 (100), 58 (98); HRMS (ESI): calcd for $C_{12}H_{18}O_3Na$ 233.1148; found 233.1150. $[\alpha]_D^{20}$ −19.7 ($CHCl_3$, *c* 70 mg/mL).

4.14. Reaction of (1*R*,2*R*,4*S*,6*S*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-yl benzoate 15 with Cp_2TiCl

According to GP1, reaction of **15** (100 mg, 0.4 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished **27** (90 mg, 90%): IR, ν=2911, 2663, 1697, 1428, 1298, 1114, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.75 (s, 3H), 1.3–2.4 (m, 5H), 4.25 (m, 1H), 4.77 (s, 2H), 5.09 (s, 1H), 5.16 (s, 1H), 5.47 (s, 1H), 7.3–8.2 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.6 (CH_3), 38.0 (CH_2), 39.2 (CH), 41.2 (CH_2), 70.6 (CH), 72.3 (CH), 101.9 (CH_2), 110.0 (CH_2), 128.4 (2CH), 129.6 (2CH), 133.0 (CH), 133.6 (C), 146.8 (C), 149.3 (C), 165.3 (C) ppm; MS EI, *m*/*z* (relative intensity): 150 (M^+−122, 3), 135 (3), 122 (2), 117 (7), 105 (98), 91 (6), 77 (18), 55 (100); HRMS (ESI): calcd for $C_{17}H_{20}O_3Na$ 295.1305; found 295.1308. $[\alpha]_D^{20}$ −18.4 ($CHCl_3$, *c* 52 mg/mL).

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Supplementary data

Experimental procedures and copies of the ^1H and ^{13}C NMR spectra for all new compounds can be found. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.093. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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10. The results obtained by Bermejo, F. and Sandoval, C. (Ref. 4b) from **5** and **9** with Ti(III) are similar, though they obtained also hydrogenation products.