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Diastereoselective synthesis of vicinal *cis*-dihydroxyheterospirocycles by one-pot epoxidation/spirocyclization of C(3)-functionalized cyclohex-2-en-1-ols†

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Spirolactones, spirotetrahydrofurans, and spiropyrrolidines containing a vicinal *cis*-diol adjacent to the spiro-carbon center are prepared by one-pot epoxidation/spirocyclization of cyclohex-2-en-1-ols bearing an ester, alcohol, or amide functional side chain at the C(3) position of the ring.

Introduction

The structurally interesting and biologically active heterospirocycles have prompted considerable attention in new synthetic developments for the construction of heterospirocyclic scaffolds. Of special interest are functionalized heterospirocycles that contain oxygen or nitrogen atoms adjacent to the spiro carbon center.[1] Most synthetic methods for building heterospirocyclic frameworks involve iron-mediated spirocyclization,[1a,b] transition metal-catalyzed ring-closing metathesis,[2] radical cyclization,[3] cleavage of heterotricyclic ring systems,[4] acid-promoted rearrangement,[5] palladium-catalyzed spirocyclization,[6] and ring closure of geminally substituted compounds.[7] However, many of these methods suffer from some drawbacks, which include the use of expensive transition metals under oxygen- and moisture-free reaction conditions. Moreover, the increased conformational rigidity and steric congestion adjacent to the spiro-carbon center often impede the ability to introduce useful functionalities into the newly formed quaternary carbon center. Therefore, construction of hetereospirocyclic frameworks containing functional groups adjacent to the spiro-carbon center is still a challenge for synthetic chemists. As part of our ongoing efforts to synthesize potential useful functionalized heterospirocyclic frameworks,[8] we envisaged that cyclic 2,3-epoxy-1-ols bearing a pendant oxygen or nitrogen nucleophile would be ideal substrates for the stereocontrol of the spirocyclization/ring-opening process, which leads to heterospirocycles having three contiguous stereogenic centers in a diastereoselective fashion. Herein, we report a convenient and mild approach for the diastereoselective synthesis of vicinal *cis*-dihydroxyheterospirocycles by epoxidation of cyclohex-2-en-1-ols bearing an ester, alcohol or amide functionalized side chain at the C(3) position of the ring with *m*-chloroperbenzoic acid (*m*CPBA). In this transformation, epoxidation of the olefin moiety of the C(3)-functionalized cyclohex-2-en-1-ols with *m*CPBA at 0 °C generates exclusively the *syn* cyclic C(3)-functionalized 2,3-epoxy-1-ols which, upon warming, undergo acid-promoted ring opening of the epoxide by the tethered *N*- or *O*-nucleophiles *via* an S_N2-like process to yield the vicinal *cis*-dihydroxyheterospirocyclic ring systems in a diastereoselective manner and in good to high yields under mild reaction conditions.

The requisite C(3)-esteralkyl-tethered cyclohex-2-en-1-ols **1–3** (Table 1, entries 1–3) were prepared from the corresponding 3-iodocyclohex-2-en-1-ones by 1,4-addition of the 2-carbethoxyethylcopper reagent ($EtO_2C(CH_2)_2Cu(CN)ZnI$).[9] Reduction of the resulting C(3)-esteralkyl-tethered cyclohex-2-en-1-ones with $NaBH_4$ in MeOH at 0 °C afforded substrates **1–3** in 40% to 92% yield. C(3)-3-esteralkyl-tethered cyclohex-2-en-1-ols **4** and **5** (Table 1, entries 4 and 5) were obtained through a similar route from the corresponding 3-iodocyclohex-2-en-1-ones in three steps by addition of 3-carbethoxypropylcopper reagent ($EtO_2C(CH_2)_3Cu(CN)ZnI$) followed by reduction with $NaBH_4$ in MeOH at 0 °C. C(3)-3-hydroxyalkyl-tethered cyclohex-2-en-1-ols **6** and **7** (Table 1, entries 6 and 7) were synthesized in 65% and 70% yield, respectively, by treatment of the

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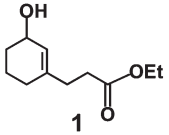
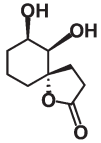
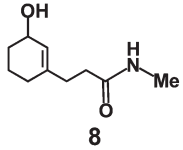
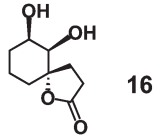
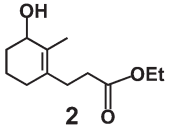
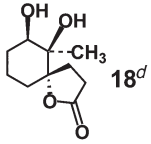
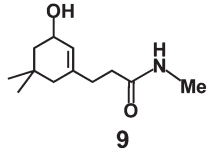
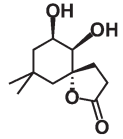
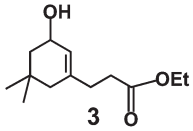
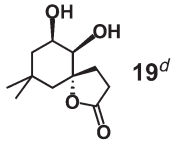
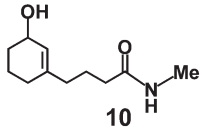
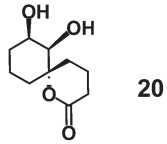
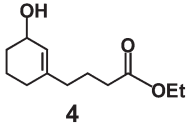
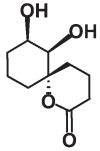
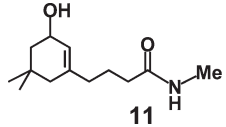
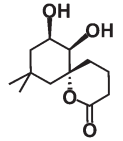
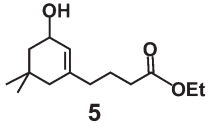
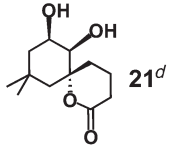
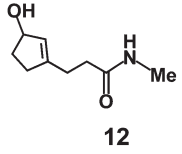
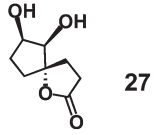
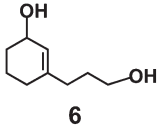
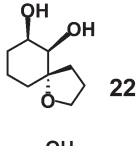
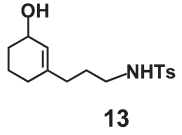
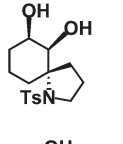
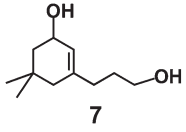
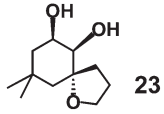
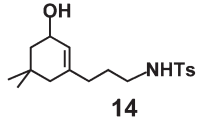
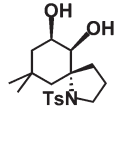
†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra for compounds **16**, **18–23** and **28–29**. CCDC 912316 (**16**), 912317 (**18**), 912318 (**19**), 912320 (**20**), 912319 (**21**), 912989 (**24**), 912990 (**28**), 912991 (**29**). For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/c3ob27352k

Table 1 One-pot epoxidation/cyclization of C(3)-functionalized cyclohex-2-en-1-ols

Entry	Substrate	Time (h)	Product	Yield[a] (%)	Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 1	3	 16[d]	43	8	 8	7	 16	64
2	 2	3	 18[d]	49	9	 9	10	 19	68
3	 3	18	 19[d]	65	10	 10	14	 20	58
4	 4	0.5[b]	 20[d]	48	11	 11	3[e]	 21	54
5	 5	0.5[b]	 21[d]	24	12	 12	9	 27	51
6	 6	2[c]	 22	29	13	 13	8	 28[d]	79
7	 7	2[c]	 23	19	14	 14	4[e]	 29[d]	51

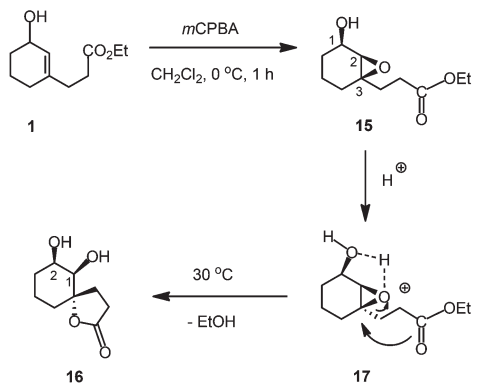
[a] All reactions were first performed at 0 °C for 1 h and then warmed to higher temperature; isolated yield by column chromatography. [b] Cyclization was performed by treatment of the *syn* epoxycyclohexanol with KOH in refluxing MeOH/H_2O. [c] Both epoxidation and cyclization steps were performed in an ice bath. [d] Structures are confirmed by X-ray diffraction analysis. [e] The cyclization was performed in 1,2-dichloroethane at 84 °C.

corresponding C(3)-2-carbethoxyethylcyclohex-2-en-1-ones with 1.2 equiv. of diisobutylaluminum hydride in ether at 0 °C for 1 h followed by aqueous workup. C(3)-methylamidoalkyl-tethered cyclohex-2-en-1-ols **8–11** (Table 1, entries 8–11) were obtained in 79% to 80% yield by reaction of the corresponding C(3)-esteralkylcyclohex-2-en-1-ols with methylamine in methanol at 30 °C for 12 h. The 5-membered ring amide **12** (Table 1, entry 12) was obtained from 3-iodocyclopent-2-en-1-one in the same manner as for the six-membered ring substrate **8**. Finally, C(3)-3-*N*-tosylalkyl-tethered cyclohex-2-en-1-ols **13** and **14** (Table 1, entries 13 and 14) were synthesized from the corresponding 3-iodocyclohex-2-en-1-ones in three steps by 1,4-addition of 2-cyanoethylcopper reagent $(NC(CH_2)_2Cu(CN)ZnI)$, reduction with $LiAlH_4$, and tosylation with TsCl in base.

Results and discussion

We first examined the epoxidation/spirocyclization reaction of compound **1** with *m*CPBA (70% in water, *vide infra*). Treatment of **1** with 1.2 equiv. of *m*CPBA in CH_2Cl_2 at 0 °C in the air for 1 h gave the *syn* 2,3-epoxycyclohexan-1-ol derivative **15** as the only diastereomer in 74% yield (Scheme 1). The stereochemistry assignment for **15** as the *syn* isomer is based on ^1H NMR analysis. The chemical shift value for H_2 and coupling constant $J_{1,2}$ for **15** were determined as 3.16 (doublet, $J_{1,2}$ = 3.2 Hz). The coupling constant of H_1–H_2 ($J_{1,2}$) of 3.2 Hz agrees with the 3.4 Hz coupling constant found for the similar neighboring protons of the *syn* 2,3-epoxy-3-methylcyclohexan-1-ol, compared to the 0–1 Hz observed when these protons are *trans*.[10] Delightfully, epoxidation/spirolactonization of **1** occurred when the epoxidation was first performed at 0 °C and the resulting reaction mixture was then stirred at a higher temperature and for an extended reaction time. Thus, treatment of **1** with 1.2 equiv. of *m*CPBA in CH_2Cl_2 at 0 °C in the air for 1 h followed by stirring the reaction mixture at 30 °C for 3 h resulted in the direct formation of 6,7-dihydroxy-1-oxaspiro [4.5]decan-2-one (**16**) as a single diastereomer in 43% yield. The reaction path was speculated as follows (Scheme 1). *m*-Chlorobenzoic acid generated during the epoxidation process would protonate the oxirane to give the oxonium species **17**. It is suggested that intramolecular hydrogen bonding from the OH and the *syn* epoxide may play an important role in both the regio- and stereoselectivity of the spirocyclization. Due to the steric congestion at the C(2) position, only 5-*exo-tet* ring-closure[11] of the pendant ester group to the quaternary carbon center of the protonated oxirane was observed. Moreover, attack of the nucleophile to the oxirane is a concerted process,[12] occurring solely from the less hindered face, leading to the γ-spirolactone ring system with the relative stereochemistry depicted in **16**. No fused bicyclic lactones resulting from the disfavored 6-*endo-tet* ring-closure[11] were detected in the 400 MHz ^1H NMR spectrum of the crude mixture. The intriguing feature of this process is that the epoxidation and spirolactonization proceeded successively to generate **16** with complete stereocontrol of the spiro-carbon and two adjacent carbinol carbons. It is noteworthy that the previous known procedure for the synthesis of γ-spirolactones required epoxidation of methylenecycloalkanes followed by addition of aluminum ester enolates to provide the cyclic hydroxyester, which produced γ-spirolactones upon treatment with *p*-TsOH.[13]

^1H NMR studies provide evidence to support the structure assignments for **16**. The peak at 3.72 as a doublet, J = 2.9 Hz, is assigned to H_2. The coupling constant of H_1–H_2 ($J_{1,2}$) of 2.9 Hz is close to the 3.0 Hz coupling constant for the similar vicinal *cis* protons of proto-quercitol compared to the 9–11 Hz observed when these protons are *trans*.[14] The relative stereochemistry of **16** is further secured by X-ray crystallographic analysis (Fig. 1). An additional methyl group at the C(2) position of the ring, for example in **2**, did not interfere with the epoxidation/spirolactonization process and afforded the desired vicinal *cis*-γ-dihydroxyspirolactone **18**[15] in 49% yield after chromatography on silica gel. However, substrate **3** with a geminal dimethyl group at the C(5) position of the ring required a longer reaction time (18 h) at 30 °C to ensure completion and produced the vicinal *cis*-γ-dihydroxyspirolactone **19** in 65% yield.[15] Attempts to obtain vicinal *cis*-δ-dihydroxylactone derivatives *via* sequential epoxidation/spirolactonization of esters **4** and **5** with *m*CPBA have been unsuccessful. Fortunately, treatment of **4** and **5** (Table 1, entries 4 and 5) with



Scheme 1 Plausible mechanism for the formation of compound **16** *via* epoxidation/spirocyclization of **1**.

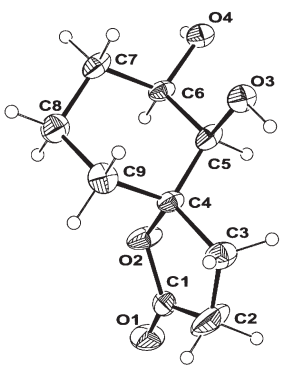


Fig. 1 X-ray crystallographic structure of **16**.

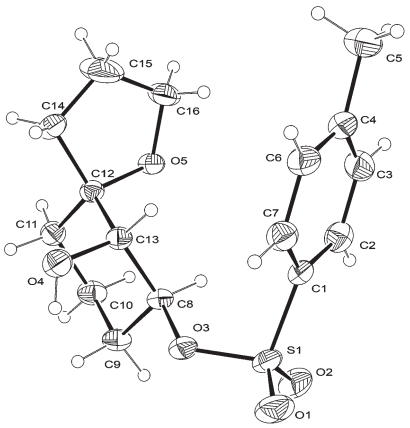
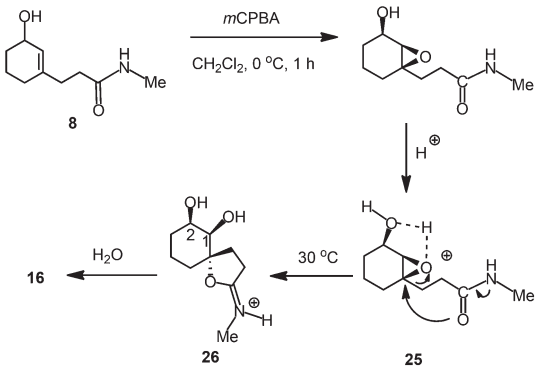


Fig. 2 X-ray crystallographic structure of **24**.



Scheme 2 Plausible mechanism for the formation of compound **16** *via* epoxidation/spirocyclization of **8**.

*m*CPBA in CH_2Cl_2 at 0 °C afforded the corresponding epoxides which upon treatment with KOH in refluxing methanol–water for 30 min (to give carboxylates) yielded vicinal *cis*-δ-dihydroxylactones **20**[15] and **21**[15] in 48% and 24% yields, respectively, as the only stereoisomer in each case. C(3)-3-hydroxyalkyl cyclohex-2-en-1-ols **6** and **7** also underwent epoxidation/spirocyclization with *m*CPBA in CH_2Cl_2 at 0 °C in the air for 2 h to produce the vicinal *cis*-dihydroxyspirofurans **22** and **23**, albeit only in 29% and 19% yields, respectively (Table 1, entries 6 and 7). The stereochemistry of the oxaspirocycle **22** was further established by X-ray diffraction analysis of the monotosylate derivative **24**[15] (Fig. 2). Next, we turned our efforts to the epoxidation/spirolactamization of C(3)-3-amidoalkyl-tethered cyclohex-2-en-1-ol **8** (Table 1, entry 8). Surprisingly, the methylamide **8** did not give any of the desired γ-dihydroxyspirolactams upon treatment with *m*CPBA in CH_2Cl_2 at 0 °C in the air for 1 h and then 30 °C for 7 h. The product, isolated in 64% yield, was identical spectroscopically to the vicinal *cis*-γ-dihydroxyspirolactone **16**. The formation of **16** from amide **8** may suggest that *anti* attack of the pendant amide oxygen at the quaternary carbon center of the protonated epoxide **25** gave the intermediate **26** (Scheme 2). Hydrolysis of the iminium cation generated the vicinal *cis*-γ-dihydroxyspirolactone **16**. However, amides **9–11** needed higher reaction temperatures and longer reaction times for cyclization to produce the vicinal *cis*-dihydroxyspirolactones **19–21** in 54% to 68% yields (Table 1, entries 9–11). The five-membered ring amide **12** also underwent epoxidation/spirocyclization with *m*CPBA to afford 6,7-dihydroxy-1-oxaspiro[4.4]nonan-2-one (**27**) in 51% isolated yield (Table 1, entry 12). Finally, vicinal *cis*-dihydroxyspiropyrrolidines were available *via* an epoxidation/spirocyclization process. Thus, treatment of C(3)-3-tosylpropylcyclohex-2-en-1-ol **13** with *m*CPBA in dichloroethane at 0 °C in the air for 1 h and 30 °C for 8 h produced the vicinal *cis*-dihydroxyazaspiro[4.5]decane derivative **28**[15] as the only diastereomer isolated in 79% yield (Table 1, entry 13). In addition, the epoxidation/spirocyclization of substrate **14** bearing geminal dimethyl groups at the C(5) position of the ring required a spirocyclization step at a higher reaction temperature (*ca.* 84 °C) in dichloroethane for 4 h to produce the vicinal *cis*-dihydroxyspiropyrrolidine derivative **29**[15] in 51% isolated yield.

Conclusions

In conclusion, we have shown a convenient one-pot synthesis of γ-spirolactone, δ-spirolactone, oxaspiro[4.5]decane, and azaspiro[4.5]decane frameworks containing vicinal *cis*-dihydroxy groups adjacent to the spiro-carbon center *via* epoxidation/spirocyclization of C(3)-functionalized cyclohex-2-en-1-ols. The heterocyclic skeletons with three contiguous stereocenters are formed in a diastereoselective fashion. Further transformation of these vicinal *cis*-dihydroxyheterospirocycles into more complex structures is currently underway in our laboratories.

Experimental sections

Typical procedure for the synthesis of *cis* vicinal dihydroxyheterospirocycles *via* epoxidation/spirolactonization of C(3)-functionalized cyclohex-2-en-1-ols

To a solution of C(3)-2-carbethoxypropylcyclohex-2-en-1-ol (**1**) (0.1 g, 0.5 mmol) in 4 mL of CH_2Cl_2 at 0 °C under the air was added 0.13 g *m*CPBA (70% in water, 0.75 mmol). The reaction mixture was allowed to stir at 0 °C until no starting substrate was detected by TLC (*ca.* 1 h). The reaction mixture was allowed to stir at 30 °C until no epoxide was detected by TLC (*ca.* 3 h). The mixture was then quenched with saturated aqueous sodium bicarbonate solution followed by addition of CH_2Cl_2 (50 mL). The resultant mixture was washed with water (50 mL × 3) and brine (50 mL × 3), dried over anhydrous magnesium sulfate (10 g), and concentrated to give the crude mixture. The residue was purified *via* flash column chromatography (silica gel, 2 : 1 ethyl acetate–hexanes) to give **16** (0.04 g, 0.21 mmol).

(±)(5*S*,6*R*,7*R*)-6,7-Dihydroxy-1-oxaspiro[4.5]decan-2-one (16). 43%; white solid, mp 121–123 °C; IR (CH_2Cl_2) 3496, 3334, 2946, 2871, 1756, 1418, 1248, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.11–4.03 (m, 1 H), 3.73 (d, J = 3.0 Hz, 1 H), 2.65–2.52

(m, 3 H), 2.05–1.95 (m, 1 H), 1.87–1.79 (m, 1 H), 1.77–1.57 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 88.7, 73.3, 69.6, 32.5, 29.0, 28.4, 28.2, 18.3; ESIMS *m*/*z* (%) 209 ([M + Na]$^+$, 90), 204 (6); HRMS (ESI) *m*/*z* calcd for $C_9H_{14}O_4Na$ 209.0790, found 209.0789. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

(±)(5*S*,6*R*,7*R*)-6,7-Dihydroxy-6-methyl-1-oxaspiro[4.5] decan-2-one (18). In a typical procedure (**2**, 0.11 g, 0.50 mmol), after the initial epoxidation, the reaction was then performed at 30 °C for 3 h and the crude mixture was purified by flash column chromatography (silica gel, 33% ethyl acetate–hexanes) to give **18** (0.05 g, 0.25 mmol, 49%) as a white solid: mp 206–207 °C; IR (CH_2Cl_2) 3418, 2922, 2841, 1765, 1660, 1451, 1370, 1026, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (t, *J* = 4.5 Hz, 1 H), 2.66–2.54 (m, 3 H), 2.06 (s, 1 H), 1.94–1.82 (m, 2 H), 1.79 (d, *J* = 4.7 Hz, 2 H), 1.78–1.72 (m, 2 H), 1.72–1.60 (m, 4 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, dimethyl Sulfoxide-d_6) δ 177.5, 90.0, 74.3, 72.4, 34.0, 29.6, 28.7, 28.2, 19.5, 19.4; EIMS *m*/*z* (%) 201 ([M + H]$^+$), 183 (53), 165 (70); HRMS (EI) *m*/*z* calcd for $C_{10}H_{17}O_4$ 201.1127, found 201.1124. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

(±)(5*R*,6*R*,7*R*)-6,7-Dihydroxy-9,9-dimethyl-1-oxaspiro[4.5] decan-2-one (19). In a typical procedure (**3**, 0.11 g, 0.50 mmol), after the initial epoxidation, the reaction was then performed at 30 °C for 18 h and the crude mixture was purified by flash column chromatography (silica gel, 33% ethyl acetate–hexanes) to give **19** (0.07 g, 0.33 mmol, 65%) as a white solid: mp 154–156 °C; IR (CH_2Cl_2) 3429, 2952, 1760, 1422, 1238, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (dt, *J* = 10.4 Hz, *J* = 3.6 Hz, 1 H), 3.63 (d, *J* = 2.2 Hz, 1 H), 2.77 (br s, 1 H), 2.62–2.45 (m, 3 H), 2.24 (br s, 1 H), 1.97–1.85 (m, 1 H), 1.67 (d, *J* = 14.7 Hz, 1 H), 1.59 (t, *J* = 12.4 Hz, 1 H), 1.51–1.40 (m, 2 H), 1.08 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 88.4, 72.4, 67.0, 43.4, 39.7, 33.2, 31.2, 31.1, 27.6, 27.5; FABMS *m*/*z* (%) 215 ([M + H]$^+$, 35), 179 (40), 136 (70), 107 (29); HRMS (FAB) *m*/*z* calcd for $C_{11}H_{19}O_4$ 215.1283, found 215.1283. Crystals suitable for X-ray diffraction analysis were grown from MeOH and hexanes.

(±)(6*S*,7*R*,8*R*)-7,8-Dihydroxy-1-oxaspiro[5.5]undecan-2-one (20). In a typical procedure (**10**, 0.20 g, 1.00 mmol), after the initial epoxidation, the reaction was performed at 30 °C for 14 h and the crude mixture was purified by flash column chromatography (silica gel, 50% ethyl acetate–hexanes) to give **20** (0.12 g, 0.58 mmol, 58%) as a white solid: mp 125–126 °C; IR (CH_2Cl_2) 3432, 3333, 2950, 1705, 1247, 1112, 1056, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (br s, 1 H), 3.72 (br s, 1 H), 3.23 (s, 1 H), 2.86 (s, 1 H), 2.51 (t, *J* = 6.4 Hz, 2 H), 2.07–1.82 (m, 3 H), 1.82–1.76 (m, 2 H), 1.76–1.57 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 86.0, 73.4, 68.7, 31.8, 29.8, 27.9, 18.1, 15.9; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.57; H, 5.68; N, 9.82. EIMS *m*/*z* (%) 201 (10), 182 (17), 165 (14), 143 (79), 131 (39), 113 (100), 97 (18), 85 (19), 70 (60); HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}O_4Na^+$ 223.0941, found 223.0957. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

(±)(6*R*,7*R*,8*R*)-7,8-Dihydroxy-10,10-dimethyl-1-oxaspiro [5.5] undecan-2-one (21). In a typical procedure (**11**, 0.22 g, 1.00 mmol), after the initial epoxidation, the reaction was then performed in 1,2-dichloroethane at 84 °C for 3 h and the crude mixture was purified by flash column chromatography (silica gel, 33% ethyl acetate–hexanes) to give **21** (0.12 g, 0.54 mmol, 54%) as a white solid: mp 158–159 °C; IR (CH_2Cl_2) 3374, 2953, 1715, 1366, 1264, 1051, 1002, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 1 H), 3.67 (s, 1 H), 3.44 (br s, 2 H), 2.52–2.48 (m, 2 H), 1.97–1.86 (m, 4 H), 1.57–1.44 (m, 4 H), 1.13 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 86.6, 72.9, 66.3, 43.4, 39.9, 33.9, 31.1, 30.3, 29.4, 27.9, 15.6; EIMS *m*/*z* (%) 210 (4), 182 (6), 171 (16), 165 (27), 147 (16), 136 (25), 125 (63), 113 (100), 97 (59), 85 (40); HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}O_4$ 228.1362, found 228.1371. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

(±)(5*S*,6*R*,7*R*)-1-Oxaspiro[4.5]decane-6,7-diol (22). In a typical procedure (**6**, 0.46 g, 2.92 mmol), the reaction was performed at 0 °C for 2 h and the crude mixture was purified by flash column chromatography (silica gel, 50% ethyl acetate–hexanes) to give **22** (0.12 g, 0.85 mmol, 29%) as a colorless oil; IR (CH_2Cl_2) 3418, 2945, 1640, 1451, 1060, 997, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 3.98–3.95 (m, 1 H), 3.80 (t, *J* = 6.7 Hz, 2 H), 3.55 (d, *J* = 2.6 Hz, 1 H), 3.26 (br s, 2 H), 2.09 (dt, *J* = 12.4, 7.9 Hz, 1 H), 1.90 (quin, *J* = 6.7 Hz, 2 H), 1.71–1.49 (m, 6 H), 1.35 (dt, *J* = 12.6, 4.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 84.9, 74.5, 69.8, 67.4, 33.5, 31.6, 28.2, 25.5, 19.2; EIMS *m*/*z* (%) 172 (M$^+$), 154 (8), 123 (9), 115 (8), 97 (100), 85 (28), 70 (13), 55 (35); HRMS (EI) *m*/*z* calcd for $C_9H_{16}O_3$ 172.1099, found 172.1097.

(±)(5*R*,6*R*,7*R*)-9,9-Dimethyl-1-oxaspiro[4.5]decane-6,7-diol (23). In a typical procedure (**7**, 0.22 g, 1.22 mmol), the reaction was performed at 0 °C for 2 h and the crude mixture was purified by flash column chromatography (silica gel, 50% ethyl acetate–hexanes) to give **23** (0.05 g, 0.23 mmol, 19%) as a white solid, mp 80–82 °C; IR (CH_2Cl_2) 3438, 2072, 1639 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) 4.09 (dt, *J* = 8.8, 2.9 Hz, 1 H), 3.81 (t, *J* = 7.1 Hz, 2 H), 3.50 (s, 1 H), 3.19 (s, 2 H), 2.10 (dt, *J* = 12.6, 7.4 Hz, 1 H), 1.85 (quin, *J* = 7.1 Hz, 2 H), 1.63–1.37 (m, 4 H), 1.24 (d, *J* = 14.3 Hz, 1 H), 1.06 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 85.5, 73.9, 68.0, 42.6, 40.5, 36.2, 34.0, 31.7, 27.6, 24.9. EIMS *m*/*z* (%) 201 (12), 183 (74), 165 (31), 154 (100), 136 (92), 125 (82), 107 (40), 89 (41); HRMS (EI) *m*/*z* calcd for $C_{11}H_{21}O_3^+$ 201.1491, found 201.1487.

(±)(5S,6R,7R)-6,7-Dihydroxy-1-oxaspiro[4.4]nonan-2-one (27). In a typical procedure (**12**, 0.33 g, 1.93 mmol), after the initial epoxidation, the reaction was performed at 30 °C for 9 h and the crude mixture was purified by flash column chromatography (silica gel, 3% methanol–ethyl acetate) to give **27** (0.17 g, 0.99 mmol, 51%) as a yellow oil; IR (CH_2Cl_2) 3418, 2946, 1760, 1642, 1416, 1031, 660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (q, *J* = 4.7, 1 H), 4.03 (br s, 1 H), 3.87 (d, *J* = 4.6, 1 H), 3.55 (br s, 1 H), 2.64–2.44 (m, 3 H), 2.07–1.84 (m, 4 H), 1.68–1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 94.5, 76.8, 71.5, 33.3, 29.1, 28.8, 27.8; EIMS *m*/*z* (%) 171 (M$^+$, 0.09), 99 (21), 98 (90), 83 (26), 81 (44), 71 (22), 70 (36), 69 (21),

60 (37), 58 (25), 57 (68), 56 (57), 55 (100), 53.0 (30); HRMS (EI) *m*/*z* calcd for $C_8H_{13}O_4$ 171.0814, found 171.0889.

(±)(5*S*,6*S*,7*R*)-1-Tosyl-1-azaspiro[4.5]decane-6,7-diol (28). In a typical procedure (**13**, 0.38 g, 1.23 mmol), after the initial epoxidation, the reaction was performed at 30 °C for 8 h and the crude mixture was purified by flash column chromatography (silica gel, 33% ethyl acetate–hexanes) to give **28** (0.32 g, 1.00 mmol, 79%) as a white solid: mp 172–173 °C; IR (CH_2Cl_2) 3448, 2936, 2372, 2346, 1320, 1150, 1092, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 4.51 (m, 1 H), 4.17 (d, J = 2.2 Hz, 1 H), 3.33–3.26 (m, 2 H), 2.57–2.52 (m, 1 H), 2.42 (s, 3 H), 2.76 (m, 1 H), 2.15–2.08 (m, 1 H), 1.88–1.49 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.2, 129.6, 127.1, 73.5, 72.6, 70.8, 49.4, 34.9, 32.0, 30.3, 23.3, 21.5, 18.5; EIMS *m*/*z* (%) 325 (M^+, 5), 250 (34), 173 (28), 173 (12), 171 (11), 170 (100), 155 (14), 96 (27), 91 (44), 65 (17); HRMS (EI) *m*/*z* calcd for $C_{16}H_{23}NSO_4$ 325.1348, found 325.1357. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

±(5*R*,6*S*,7*R*)-9,9-Dimethyl-1-tosyl-1-azaspiro[4.5]decane-6,7-diol (29). In a typical procedure (**14**, 0.45 g, 1.34 mmol), after the initial epoxidation, the reaction was performed in 1,2-dichloroethane at 84 °C for 4 h and the crude mixture was purified by flash column chromatography (silica gel, 50% ethyl acetate–hexanes) to give **29** (0.24 g, 0.68 mmol, 79%) as a white solid: mp 134–135 °C; IR (CH_2Cl_2) 3454, 2908, 1613, 1322, 1151, 1092, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 4.55 (t, J = 4.3 Hz, 1 H), 4.22 (s, 1 H), 3.40–3.35 (m, 1 H), 3.14 (dd, J = 7.2, 15.6 Hz, 1H), 2.72–2.66 (m, 1 H), 2.43 (s, 3 H), 2.37–2.33 (m, 2 H), 2.13 (s, 1 H), 1.96–1.86 (m, 2 H), 1.80–1.70 (m, 2 H), 1.53 (d, J = 11.0 Hz, 1 H), 1.45 (dd, J = 2.6, 13.5 Hz, 1 H), 1.17 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.1, 129.5, 127.2, 73.8, 73.3, 71.7, 48.5, 47.8, 42.1, 35.0, 34.7, 31.9, 28.6, 24.1, 21.4; MS (EI) *m*/*z* (%) 353 (M^+, 8), 279 (11), 278 (60), 250 (10), 238 (11), 198 (100), 173 (11), 155 (24), 124 (19), 123 (13), 91 (51), 84 (26); HRMS (EI) *m*/*z* calcd for $C_{18}H_{27}SNO_4$ 353.1662, found 353.1663. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

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