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Enantioselective route to 3-vinylidene tetrahydropyrans and 3-vinylidene oxepanes based on a silyl-Prins cyclization

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Abstract

A general method has been developed for the asymmetric synthesis of 3-vinylidene tetrahydropyrans and 3-vinylidene oxepanes based on the Lewis acid-catalyzed intramolecular reactions of oxocarbenium ions with propargylsilanes. The observed excellent diastereoselectivity and a high asymmetric induction offer a new synthetic method with a wide scope and generality.

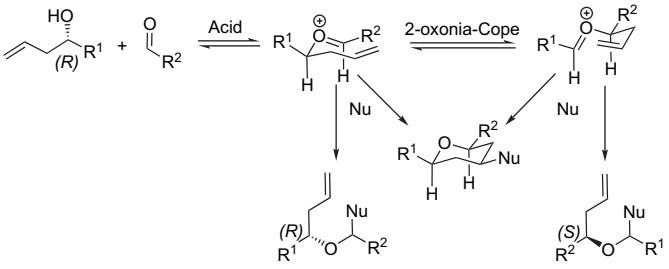
Keywords: Propargylsilanes; Tetrahydropyrans; Oxepanes; Asymmetric synthesis; Prins cyclization

1. Introduction

The 2,6-disubstituted tetrahydropyran and 2,7-disubstituted oxepane scaffolds occur in many natural products exhibiting important biological activities.[1] The syntheses of such moieties have been achieved through a wide range of methods that have been recently reviewed.[2] One of them, the intramolecular Prins reaction has been recognized as a powerful synthetic transformation to assemble six- and seven-membered ring ethers.[3] An important advantage of this methodology is the possibility of construction of cyclic ethers in one step from the homoallylic alcohols and simple aldehydes under acid catalysis. However, if the secondary homoallylic alcohols are used then the 2-oxonia-Cope rearrangement can take place as a competitive process (Scheme 1).[4] An important consequence of the Cope rearrangement is partial or total racemization of the final products when enantiomerically enriched starting materials are used.

While the Prins reaction has shown a great potential in organic synthesis, there are only a few reports regarding the enantioselective Prins cyclization, which could play a useful role in the synthesis of optically active oxygenated heterocycles.[5]

A considerable effort has been directed toward improving the efficiency of the Prins cyclization, primarily by attempts to increase nucleophilicity of the alkene reagent.[3] A number of prior reports documented the utility of allylsilanes,[6] vinylsilanes,[7] and allenylmethylsilanes[8] as intramolecular traps for the generated oxocarbenium ions. Recently, we have reported a highly diastereoselective approach to the *cis*-2,6-disubstituted-3-vinylidene tetrahydropyrans based on the Lewis acid-catalyzed intramolecular reactions of oxocarbenium ions with propargylsilanes.[9] In this paper, we extend this methodology to the enantioselective synthesis of tetrahydropyran and oxepane derivatives.



Scheme 1.

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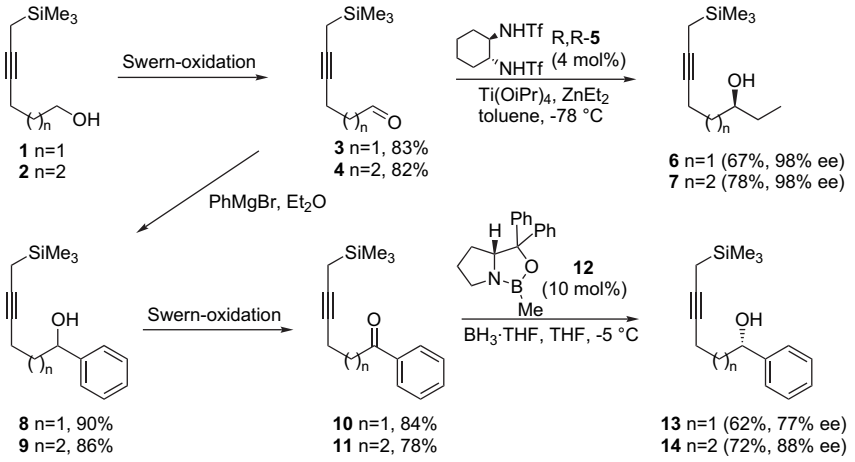


Scheme 2.

2. Results and discussion

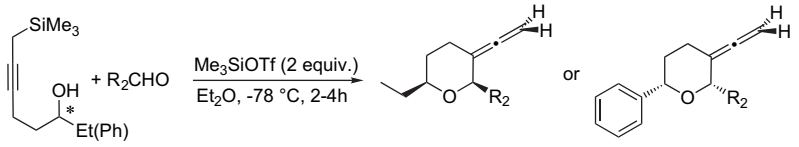
The synthesis of enantiomerically pure propargylsilanes **6**,**7**,**13**, and **14** suitable for the preparation of oxygenated heterocycles is shown in Scheme 2.

Alcohols **6** and **7** were prepared via the catalytic enantioselective addition of diethylzinc to aldehydes **3** and **4**. According to the known protocol[10] the diamine triflate (*R*,*R*)-**5** was treated with $Ti(O^iPr)_4$ to form the titanium complex that was used to activate the diethylzinc. The nonracemic alcohols **13** and **14** were obtained via the enantioselective reduction of corresponding ketones **10** and **11** by $BH_3\cdot THF$ in the presence of (*R*)-*B*-methyl CBS catalyst **12**.[11] The enantiomeric purity of these products was determined by ^{19}F NMR spectroscopic analysis of the corresponding Mosher esters.[12]

With suitable propargylsilanes in hand, we initiated our study using conditions reported in our earlier work.[9] Thus, we treated alcohols **6** and **13** and selected aldehydes with TMSOTf in Et_2O at −78 °C (Table 1).

In almost all cases, the Prins cyclization with various aldehydes proceeded to give the 2,6-disubstituted-3-vinylidene THP in a good yield and an excellent stereoselectivity. Both aliphatic (entries 1–6) and aromatic (entries 7–9) substituted propargylsilanes were effective substrates to provide the expected nonracemic *cis*-2,6-tetrahydropyrans. The observed cis-stereoselectivity can be explained by the formation of an initial (*E*)-oxocarbenium ion.[13] The cis-configuration was assigned based on the NOE enhancement observed between H_2 and H_6 protons.[9] In the reaction of aromatic substituted propargylsilanes (entries 7–9), partial racemization is observed. Such a result could be rationalized by the formation of achiral benzylic cation from the initial alcohol **13** or the related oxocarbenium ion.[4c] Due to this mechanism, Prins cyclization reactions utilizing an electron-rich aromatic substrate are often problematic.[4]

Table 1
Prins cyclization of **6** and **13** with selected aldehydes

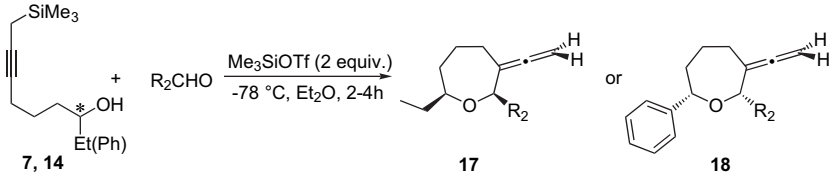


6, 13 15 16

Entry	Product	R_2	Yield[a] (%)	dr[b] (cis/trans)	ee[c] (%)
1	**15a**	C_6H_5	83	Cis only	98
2	**15b**	*p*-$MeOC_6H_4$	90	3:1	97 (cis)
3	**15c**	*p*-BrC_6H_4	85	Cis only	97
4	**15d**	*p*-$NO_2C_6H_4$	73	Cis only	98
5	**15e**	$C_6H_5CH{=}CH$	92	10:1	94 (cis)
6	**15f**	C_6H_5 $(CH_2)_2$	90	Cis only	95
7	**16a**	C_6H_5	92	Cis only	70
8	**16b**	*p*-BrC_6H_4	87	Cis only	67
9	**16c**	C_6H_5 $(CH_2)_2$	84	Cis only	68

[a] Isolated yields following column chromatography.
[b] Ratio calculated from ^1H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC analysis employing DAICEL chiral columns.

Table 2
Prins cyclization of **7** and **14** with selected aldehydes



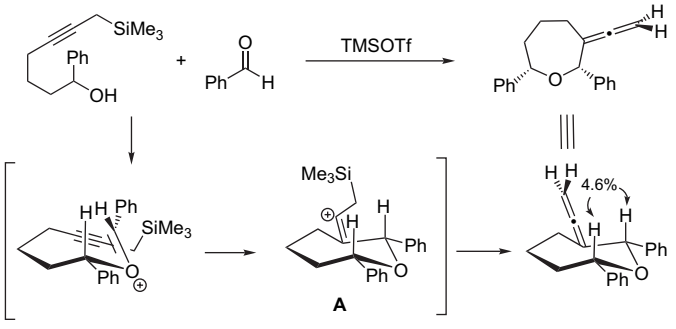
7, 14 17 18

Entry	Product	R_2	Yield[a] (%)	dr[b] (cis/trans)	ee[c] (%)
1	**17a**	C_6H_5	92	Cis only	97
2	**17b**	*p*-$MeOC_6H_4$	90	Cis only	90
3	**17c**	*p*-$NO_2C_6H_4$	75	Cis only	98
4	**17d**	$C_6H_5CH_2$	80	Cis only	95
5	**17e**	C_6H_5 $(CH_2)_2$	89	Cis only	98
6	**17f**	2-Furyl	81	Cis only	98
7	**18a**	C_6H_5	95	Cis only	80
8	**18b**	*p*-$NO_2C_6H_4$	75	Cis only	83
9	**18c**	C_6H_5 $(CH_2)_2$	89	Cis only	85

[a] Isolated yields following column chromatography.
[b] Ratio calculated from ^1H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC analysis employing DAICEL chiral columns.

The scope of this transformation was further extended to the reaction leading to compounds with a larger ring size. The suitable propargylsilanes **7** and **14** were prepared using similar strategy as described earlier, starting from alcohol **2**.

In the case of the propargylsilanes **7** and **14** with a longer chain, the intramolecular Prins reaction, under standard conditions (2.0 equiv TMSOTf in Et_2O at −78 °C), led to the 3-vinylidene oxepanes. The products were obtained as single diastereomers in a good to excellent yield and with a high stereoselectivity (Table 2). The relative cis-configuration was established with NOE experiments. The 4.6% enhancement was observed for the C2 proton on irradiation of the C7 proton in oxepane **18a** (Scheme 3).



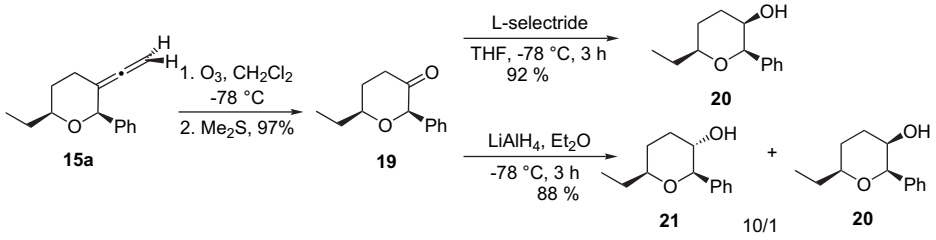
Scheme 3.

The stereochemical outcome of this reaction is in accord with the previous observations[14] and with the expectation that cyclization should occur via transition state **A** with Ph and Ph disposed equatorially (Scheme 3).

To illustrate the synthetic versatility of the obtained cyclic compounds, we performed a series of further synthetic transformations of these intermediates. Thus, ozonolysis of **15a** led to the ketone **19**, which in the presence of L-Selectride® at low temperature gave an alcohol **20** as a single detectable isomer whereas reduction with $LiAlH_4$ furnished a mixture of alcohols **20** and **21** (Scheme 4). No evidence of epimerization of the tetrahydropyran **15a** during the ozonolysis/reduction steps was detected by NMR spectroscopy.

3. Conclusions

In conclusion, we have developed a new method for the synthesis of optically active oxygenated heterocycles based on the Lewis acid-catalyzed intramolecular reactions of oxocarbenium ions with propargylsilanes. The present method is applicable to the asymmetric synthesis of a variety of tetrahydropyrans and oxepanes. The utility of the present method for further total synthesis of selected natural products is currently under investigation.



15a 19 20 21 10/1 20

Scheme 4.

4. Experimental

4.1. General

Column chromatography was performed on Merck silica gel, grade 60 (230–400 mesh). TLC plates were visualized with UV and/or staining with phosphomolybdic acid. ^{1}H NMR spectra were recorded on a Bruker AM500 (500 MHz) spectrometer and the chemical shifts are reported in parts per million with TMS as an internal standard (δ=0 ppm). ^{13}C NMR spectra were recorded at 125 MHz on a Bruker AM500 spectrometer. The chemical shifts are reported in parts per million relative to the center of the triplet at 77.0 ppm for $CDCl_3$. Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR-1600 infrared spectrophotometer. High-resolution mass spectra were recorded on a Mariner PerSeptive Biosystems mass spectrometer with time-of-flight (TOF) detector. HPLC analyses were performed on HPLC system equipped with chiral stationary phase columns, detection at 254 nm. Unless stated otherwise, all reagents and solvents were purchased from commercial sources and used without additional purification. The following known compounds were prepared by literature procedures: 6-(trimethylsilyl)hex-4-ynal (**3**),[15] 7-(trimethylsilyl)hept-5-ynal (**4**),[16] 1-phenyl-6-(trimethysilyl)hex-4-yn-1-ol (**8**),[15] 1-phenyl-7-(trimethysilyl)hept-5-yn-1-ol (**9**).[15]

4.1.1. (S)-8-(Trimethylsilyl)oct-6-yn-3-ol (*6*)

Ditriflate (*R*,*R*-**5**) (22 mg, 0.058 mmol) in toluene (2 mL) was treated with Ti(O^{i}Pr)$_4$ (853 mg, 3.0 mmol) and the mixture was stirred at 40 °C for 1 h. The mixture was cooled to −78 °C and diethylzinc (1 M in hexane, 3 mL) was added dropwise. A dark red solution was obtained, which was treated dropwise with aldehyde (**3**) (504 mg, 3.0 mmol) in toluene (2 mL) and the mixture was stirred at −78 °C for 24 h. The reaction was quenched with 1 N HCl (5 mL) and extracted with ether. The ether phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexane/ethyl acetate 95:5) to furnish (*S*)-**6** (382 mg, 67%) as a colorless oil with an enantiomeric excess of 98% determined by the Mosher's method. $[\alpha]_D$ +16.2 (*c* 1.0, CH_2Cl_2); IR (neat) 3368, 1249, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.68 (m, 1H), 2.38, 2.22 (m, 2H), 1.80 (d, *J*=4.5 Hz, 1H (OH)), 1.66 (m, 1H), 1.60 (m, 3H), 1.44–1.40 (m, 2H), 0.9 (t, *J*=7.4 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 78.4, 78.3, 72.7, 35.8, 30.0, 15.6, 9.9, 6.9, −2.1; HRMS calcd for $C_{11}H_{22}OSi$ (M^+): 198.1439, found: 198.1434.

4.1.2. (S)-9-(Trimethylsilyl)non-7-yn-3-ol (*7*)

By using the procedure for the synthesis of **6**, compound **4** (634 mg, 3.0 mmol) was converted into the alcohol **7**. Chromatography (97:3 hexane/AcOEt) afforded 433 mg (78%) of a colorless oil with an enantiomeric excess of 98% determined by the Mosher's method. $[\alpha]_D$ +8.7 (*c* 0.8, CH_2Cl_2); IR (neat) 3370, 2958, 1456, 1249, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.55 (m, 1H), 2.21–2.15 (m, 2H), 1.68–1.57 (m, 2H), 1.55–1.44 (m, 4H), 1.43–1.38 (m, 3H), 0.95 (t, *J*=7.5 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 78.5, 77.7, 72.9, 36.1, 30.2, 25.5, 18.9, 9.8, 6.9, −2.1; HRMS calcd for $C_{12}H_{24}OSi$ (M^+): 212.1596, found: 212.1607.

4.1.3. 1-Phenyl-6-(trimethylsilyl)hex-4-yn-1-one (*10*)

Oxalyl chloride (0.5 mL, 5.5 mmol) in dichloromethane (15 mL) was treated with DMSO (0.85 mL, 12.5 mmol) at −78 °C. The mixture was stirred for 15 min at −78 °C, then the alcohol **8** (1.23 g, 5.0 mmol) in dichloromethane (5 mL) was added and the mixture was stirred at −78 °C for 2 h. NEt_3 (2.25 mL, 20 mmol) was added and the cooling bath was removed. After 1 h the reaction was complete (TLC monitoring). Workup with water furnished after chromatography (98:2 hexane/AcOEt) ketone **10** (1.03 g, 84%) as a colorless oil. IR (neat) 2956, 1688, 1249, 851, 690 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 7.78–7.74 (m, 2H), 7.14 (m, 1H), 7.08–7.04 (m, 2H), 2.88–2.78 (m, 2H), 2.61–2.55 (m, 2H), 1.38 (t, *J*=2.7 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ: 197.1, 137.3, 132.6, 128.5, 128.3, 78.1, 78.0, 38.6, 14.3, 7.2, −2.1; HRMS calcd for $C_{15}H_{20}ONaSi$ (M+Na)$^+$: 267.1176, found: 267.1186.

4.1.4. 1-Phenyl-7-(trimethylsilyl)hex-5-yn-1-one (*11*)

By using the procedure for the synthesis of **10**, compound **9** (260 mg, 1.0 mmol) was converted into the alcohol **11**. Chromatography (97:3 hexane/AcOEt) afforded 203 mg (78%) of a colorless oil. IR (neat) 2956, 1687, 1248, 851, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00–7.96 (m, 2H), 7.56 (m, 1H), 7.48–7.44 (m, 2H), 3.15–3.09 (m, 2H), 2.32–2.26 (m, 2H), 1.95–1.89 (m, 2H), 1.42 (t, *J*=2.7 Hz, 2H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.0, 137.1, 132.9, 128.6, 128.1, 78.5, 77.9, 37.5, 23.9, 18.6, 7.0, −2.0; HRMS calcd for $C_{16}H_{22}ONaSi$ (M+Na)$^+$: 281.1332, found: 281.1325.

4.1.5. (S)-1-Phenyl-6-(trimethylsilyl)hex-4-yn-1-ol (*13*)

To a solution of **10** (200 mg, 0.8 mmol) in 2 mL of THF at −5 °C was added 0.08 mL of 1 M solution of (*R*)-2-methyl-CBS-oxazaborolidine (**12**) (0.08 mmol) in toluene, then dropwise 1.0 mL of a 1 M solution of $BH_3\cdot$THF (1.0 mmol) in THF at −5 °C. The reaction mixture was then stirred 24 h at −5 °C and quenched with 0.5 mL of methanol. The reaction mixture was stirred 15 min at room temperature and a saturated aqueous solution of NH_4Cl (10 mL) was added. The organic phase was separated and the aqueous phase was extracted with 10 mL of AcOEt. The combined extracts were dried with Na_2SO_4 and concentrated. Silica gel chromatography of the residue (95:5 hexane/AcOEt) afforded the desired product as a colorless oil (120 mg, 62%) with an enantiomeric excess of 77% determined by the Mosher's method. $[\alpha]_D$ +2.6 (*c* 0.6, CH_2Cl_2); IR (neat) 3392, 2954, 1248, 851, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.27 (m, 5H), 6.72 (dd, *J*=8.2, 4.9 Hz, 1H), 4.20 (m, 1H), 4.06 (m, 1H), 3.81 (m, 1H), 3.72 (m, 1H), 3.32 (t, *J*=2.7 Hz, 1H), 1.92–1.84 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.4, 128.4, 127.5, 125.8, 78.6, 77.9, 73.6, 38.4, 15.7, 7.0, −2.0; HRMS calcd for $C_{15}H_{22}ONaSi$ (M+Na)$^+$: 269.1332, found: 269.1324.

*4.1.6. (S)-1-Phenyl-7-(trimethylsilyl)hept-5-yn-1-ol (**14**)*

By using the procedure for the synthesis of **13**, compound **11** (128 mg, 0.5 mmol) was converted into the alcohol **14**. Chromatography (97:3 hexane/AcOEt) afforded 88 mg (72%) of a colorless oil with an enantiomeric excess of 88% determined by the Mosher's method. $[\alpha]_D$ +1.3 (*c* 0.5, CH_2Cl_2); IR (neat) 3368, 2953, 1249, 851, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.20 (m, 5H), 4.65 (m, 1H), 2.20–2.15 (m, 2H), 1.95–1.80 (m, 3H), 1.60 (m, 1H), 1.49 (m, 1H), 1.41–1.38 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 129.6, 128.4, 127.5, 125.9, 78.4, 77.9, 74.3, 38.2, 25.6, 18.8, 6.9, −2.1; HRMS calcd for $C_{16}H_{24}ONaSi$ $(M+Na)^+$: 283.1489, found: 283.1495.

4.2. Typical experimental procedure for the trimethylsilyl trifluoromethanesulfonate mediated reaction

To a solution of propargylsilane (0.2 mmol) and aldehyde (0.4 mmol) in Et_2O (6 mL) at −78 °C, under argon, TMSOTf (0.4 mmol) was added dropwise. The reaction was stirred at −78 °C for 2–4 h. After completion of the reaction (TLC), the solution was allowed to warm to 0 °C, poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (2×10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

*4.2.1. (2R,6S)-6-Ethyl-2-phenyl-3-vinylidenetetrahydro-2H-pyran (**15a**)*

Chromatography (1:99 Et_2O/hexane) afforded 35.6 mg (83%) of a colorless oil. $[\alpha]_D$ −4.6 (*c* 1.7, CH_2Cl_2); IR (neat) 2938, 1964, 1069, 842, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.20 (m, 5H), 4.91 (t, *J*=3 Hz, 1H), 4.38–4.34 (m, 2H), 3.51 (m, 1H), 2.56 (ddd, *J*=13.7, 4.8, 2.5 Hz, 1H), 2.45 (m, 1H), 1.81 (m, 1H), 1.67 (m, 1H), 1.50–1.49 (m, 2H), 0.97 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.4, 140.3, 127.6, 127.3, 127.1, 102.6, 80.0, 79.4, 76.1, 31.3, 29.1, 29.0, 9.8; HRMS calcd for $C_{15}H_{18}O$ (M^+): 214.1358, found: 214.1360; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 8.9 min (98.9%), 10.1 min (1.1%).

*4.2.2. (2R,6S)-6-Ethyl-2-(4-methoxyphenyl)-3-vinylidene-tetrahydro-2H-pyran (cis-**15b**)*

Chromatography (1:99 Et_2O/hexane) afforded a nonseparable mixture of **15b** (*cis*)/**15b** (*trans*) in a ratio of 3:1, respectively, 44.2 mg (90%), colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ signals due to major isomer inter alia: 7.25–7.22 (m, 2H), 6.87–6.81 (m, 2H), 4.85 (t, *J*=3.1 Hz, 1H), 4.42–4.35 (m, 2H), 3.79 (s, 3H), 3.48 (m, 1H), 2.53 (ddd, *J*=13.7, 4.7, 2.5 Hz, 1H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.5, 158.8, 132.8, 128.4, 113.0, 102.8, 79.7, 79.5, 76.0, 55.3, 31.3, 29.1, 9.8; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 14.0 min (98.7%), 10.1 min (1.3%). Signals due to **15b** (*trans*) inter alia: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 5.44 (m, 1H), 4.80 (dd, *J*=10.1, 4.2 Hz, 1H), 4.72 (dd, *J*=10.1, 4.7 Hz, 1H), 3.81 (s, 3H), 3.37 (m, 1H), 0.97 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.4, 158.7, 131.7, 128.2, 113.8, 97.6, 76.5, 74.8, 71.2, 55.2, 31.6, 28.9, 25.2, 10.1; HRMS calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463, found: 244.1457.

*4.2.3. (2R,6S)-2-(4-Bromophenyl)-6-ethyl-3-vinylidene-tetrahydro-2H-pyran (**15c**)*

Chromatography (1:99 Et_2O/hexane) afforded 42.2 mg (85%), yellow oil. $[\alpha]_D$ −22.8 (*c* 0.1, CH_2Cl_2); IR (neat) 2938, 1962, 1489, 1070, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.46–7.41 (m, 2H), 7.21–7.17 (m, 2H), 4.87 (t, *J*=3 Hz, 1H), 4.39 (m, 2H), 3.49 (m, 1H), 2.54 (ddd, *J*=13.7, 4.7, 2.5 Hz, 1H), 2.42 (m, 1H), 1.81 (m, 1H), 1.65 (m, 1H), 1.50–1.47 (m, 2H), 0.96 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.2, 139.4, 130.7, 128.8, 121.1, 102.3, 79.5, 79.3, 76.5, 31.2, 29.0, 28.9, 9.8; HRMS calcd for $C_{15}H_{17}OBr$ (M^+): 292.0463, found: 292.0469; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 8.4 min (98.5%), 9.1 min (1.5%).

*4.2.4. (2R,6S)-6-Ethyl-2-(4-nitrophenyl)-3-vinylidene-tetrahydro-2H-pyran (**15d**)*

Chromatography (4:96 Et_2O/hexane) afforded 38.0 mg (73%), off white needles. Recrystallization from pentane afforded **15d** as white needles: mp 111–113 °C. $[\alpha]_D$ −27.1 (*c* 0.1, CH_2Cl_2); IR (KBr) 2938, 1964, 1345, 1057, 855, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.18–8.15 (m, 2H), 7.49–7.47 (m, 2H), 5.01 (t, *J*=3 Hz, 1H), 4.41–4.34 (m, 2H), 3.53 (m, 1H), 2.57 (ddd, *J*=13.7, 4.7, 2.5 Hz, 1H), 2.44 (m, 1H), 1.88–1.61 (m, 2H), 1.63–1.50 (m, 2H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.0, 147.6, 147.2, 127.8, 122.9, 101.9, 79.5, 78.9, 76.7, 31.2, 28.97, 28.95, 9.8; HRMS calcd for $C_{15}H_{17}O_3N$ (M^+): 259.1208, found: 259.1198; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 14.7 min (1.0%), 18.0 min (99.0%).

*4.2.5. (2R,6S)-6-Ethyl-2-styryl-3-vinylidenetetrahydro-2H-pyran (**15e**)*

Chromatography (3:97 Et_2O/hexane) afforded a mixture **15e** (*cis*) and **15e** (*trans*) in a ratio of 10:1, respectively, 42.0 mg (92%). IR (neat) 3425, 2935, 1965, 1071, 844, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ signals due to major isomer: 7.45–7.17 (m, 5H), 6.66 (dd, *J*=15.8, 0.8 Hz, 1H), 6.32 (dd, *J*=15.8, 6.4 Hz, 1H), 4.82–4.63 (m, 2H), 4.49 (m, 1H), 3.42 (m, 1H), 2.50 (ddd, *J*=13.5, 4.7, 2.4 Hz, 1H), 2.43–2.24 (m, 2H), 1.77 (m, 1H), 1.70–1.35 (m, 2H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 204.1, 139.2, 129.1, 128.7, 128.0, 126.4, 119.2, 108.1, 80.2, 79.6, 76.5, 29.9, 28.7, 28.2, 10.2; HRMS calcd for $C_{17}H_{20}O$ (M^+): 240.1514, found: 240.1522; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 9.5 min (96.8%), 11.9 min (3.2%).

*4.2.6. (2R,6S)-6-Ethyl-2-phenethyl-3-vinylidenetetrahydro-2H-pyran (**15f**)*

Chromatography (1:99 Et_2O/hexane) afforded 43.6 mg (90%), colorless oil. $[\alpha]_D$ −6.4 (*c* 0.1, CH_2Cl_2); IR (neat) 2937, 1960, 1454, 1086, 843, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.30−7.15 (m, 5H), 4.77 (dq, *J*=9.8, 4.1 Hz, 1H), 4.70 (dq, *J*=9.8, 4.5 Hz, 1H), 3.71 (m, 1H), 3.28 (m, 1H), 2.85 (m, 1H), 2.74 (m, 1H), 2.42 (ddd, *J*=13.6, 4.7, 2.3 Hz, 1H), 2.24 (m, 1H), 1.96−1.89 (m, 2H), 1.73 (ddd, *J*=13.1, 4.7, 2.2 Hz, 1H) 1.62 (m, 1H), 1.55−1.35 (m, 2H), 1.1 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.2, 142.5, 128.6, 128.2, 125.6, 101.0, 79.3, 76.3, 75.2, 34.9, 32.1, 31.8, 29.2, 28.9, 10.3; HRMS calcd for $C_{17}H_{22}O$ (M^+): 242.1671, found: 242.1665; HPLC (DAICEL CHIRALCEL OB-H, 25 cm×0.46 cm I.D., rate 0.1 mL/min, hex/IPA=99:1) 35.8 min (97.7%), 39.0 min (2.3%).

*4.2.7. (2S,6S)-2,6-Diphenyl-3-vinylidenetetrahydro-2H-pyran (**16a**)*

Chromatography (5:95 Et_2O/hexane) afforded 48.0 mg (92%), colorless oil. $[\alpha]_D$ −46.7 (*c* 0.2, CH_2Cl_2); IR (neat) 2983, 1960, 1454, 1064, 845, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.46−7.24 (m, 10), 5.16 (t, *J*=3.2 Hz, 1H), 4.68 (dd, *J*=11.4, 2.4 Hz, 1H), 4.45−4.43 (m, 2H), 2.70−2.60 (m, 2H), 2.07 (m, 1H), 1.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.6, 142.6, 139.9, 128.3, 127.6, 127.5, 127.4, 127.2, 125.9, 102.0, 80.5, 80.2, 76.4, 34.5, 29.5; HRMS calcd for $C_{19}H_{18}O$ (M^+): 262.1358, found: 262.1356; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 25.7 min (16.8%), 28.9 min (83.2%).

*4.2.8. (2S,6S)-2-(4-Bromophenyl)-6-phenyl-3-vinylidene-tetrahydro-2H-pyran (**16b**)*

Chromatography (5:95 AcOEt/hexane) afforded 50.0 mg (87%), colorless oil. $[\alpha]_D$ −45.2 (*c* 0.5, CH_2Cl_2); IR (neat) 2922, 1963, 1709, 1489, 1066, 848, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.44−7.22 (m, 9H), 5.07 (m, 1H), 4.64 (dd, *J*=11.4, 1.9 Hz, 1H), 4.46−4.44 (m, 2H), 2.67−2.55 (m, 2H), 2.08 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.5, 142.4, 139.0, 130.8, 128.9, 128.3, 127.5, 125.8, 121.3, 101.7, 80.2, 79.8, 76.7, 34.4, 29.4; HRMS calcd for $C_{19}H_{17}OBr$ (M^+): 340.0463, found: 340.0459; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=97:3) 15.1 min (83.3%), 20.9 min (16.7%).

*4.2.9. (2S,6S)-2-Phenethyl-6-phenyl-3-vinylidene-tetrahydro-2H-pyran (**16c**)*

Chromatography (5:95 AcOEt/hexane) afforded 53.4 mg (84%), yellow oil. $[\alpha]_D$ −65.0 (*c* 0.2, CH_2Cl_2); IR (neat) 2950, 1960, 1453, 1063, 845, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.08 (m, 10H), 4.78−4.66 (m, 2H), 4.40 (dd, *J*=11.3, 1.3 Hz, 1H), 3.88 (m, 1H), 2.80 (m, 1H), 2.70 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 1.99−1.90 (m, 3H), 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.4, 142.8, 142.4, 128.6, 128.4, 128.2, 127.3, 125.8, 125.6, 100.3, 79.5, 76.6, 75.8, 34.9, 34.1, 31.7, 29.3; HRMS calcd for $C_{21}H_{22}O$ $(M)^+$: 290.1671, found: 290.1680; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=97:3) 14.7 min (81.2%), 19.2 min (18.8%).

*4.2.10. (2R,7S)-7-Ethyl-2-phenyl-3-vinylideneoxepane (**17a**)*

Chromatography (1:99 Et_2O/hexane) afforded 44.3 mg (92%), yellow oil. $[\alpha]_D$ +257.8 (*c* 0.1, CH_2Cl_2); IR (neat) 2927, 1955, 1450, 1069, 847, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.47−7.21 (m, 5H), 5.21 (s, 1H), 4.79 (ddd, *J*=10.1, 3.1, 1.5 Hz, 1H), 4.70 (d, *J*=10.1 Hz, 1H), 3.52 (m, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.55−1.40 (m, 3H), 0.97 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.9, 142.8, 128.0, 127.1, 126.2, 107.2, 81.2, 80.3, 75.5, 35.9, 30.2, 29.1, 28.0, 10.3; HRMS calcd for $C_{16}H_{20}O$ (M^+): 228.1514, found: 228.1519; HPLC (DAICEL CHIRALPAK AS-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=98:2) 10.6 min (98.7%), 15.5 min (1.3%).

*4.2.11. (2R,7S)-7-Ethyl-2-(4-methoxyphenyl)-3-vinylidene-oxepane (**17b**)*

Chromatography (4:96 Et_2O/hexane) afforded 45.0 mg (90%), colorless oil. $[\alpha]_D$ +108.2 (*c* 0.1, CH_2Cl_2); IR (neat) 2938, 1954, 1478, 1075, 842, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36−7.33 (m, 2H), 6.86−6.82 (m, 2H), 5.16 (s, 1H), 4.77 (dd, *J*=10.1, 1.4 Hz, 1H), 4.69 (d, *J*=10.1 Hz, 1H), 3.78 (s, 3H), 3.50 (m, 1H), 2.24 (m, 1H), 2.11 (m, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.63−1.39 (m, 4H), 0.96 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.8, 158.8, 135.1, 127.3, 113.5, 107.3, 80.9, 80.3, 76.7, 55.5, 35.9, 30.2, 29.1, 28.1, 10.3; HRMS calcd for $C_{17}H_{22}O_2$ (M^+): 258.1619, found: 258.1628; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 10.7 min (95.0%), 13.6 min (5.0%).

*4.2.12. (2R,7S)-7-Ethyl-2-(4-nitrophenyl)-3-vinylidene-oxepane (**17c**)*

Chromatography (4:96 Et_2O/hexane) afforded 41.5 mg (75%), yellow oil. $[\alpha]_D$ +63.6 (*c* 0.3, CH_2Cl_2); IR (neat) 2931, 1955, 1520, 1346, 1077, 847, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.20−8.16 (m, 2H), 7.60−7.55 (m, 2H), 5.27 (m, 1H), 4.84 (dd, *J*=10.5, 1.5 Hz, 1H), 4.74 (d, *J*=10.5 Hz, 1H), 3.54 (m, 1H), 2.21 (m, 1H), 2.01−1.89 (m, 2H), 1.79 (m, 1H), 1.65−1.40 (m, 4H), 0.95 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.9, 150.1, 147.1, 126.8, 123.3, 106.5, 80.7, 80.4, 76.2, 35.9, 30.1, 28.8, 27.9, 10.2; HRMS calcd for $C_{16}H_{19}O_3N$ (M^+): 273.1365, found: 273.1363; HPLC (DAICEL CHIRALPAK AS-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 9.8 min (1.0%), 13.5 min (99.0%).

*4.2.13. (2R,7S)-2-Benzyl-7-ethyl-3-vinylideneoxepane (**17d**)*

Chromatography (1:99 Et_2O/hexane) afforded 39.0 mg (80%), colorless oil. $[\alpha]_D$ +72.2 (*c* 0.3, CH_2Cl_2); IR (neat) 2926, 1954, 1453, 1082, 846, 698 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ: 7.27–7.16 (m, 5H), 4.56 (dd, J=9.8, 1.3 Hz, 1H), 4.35 (d, J=9.8 Hz, 1H), 4.26 (m, 1H), 3.21 (m, 1H), 2.95 (dd, J=13.5, 7.4 Hz, 1H), 2.78 (dd, J=13.5, 6.2 Hz, 1H), 2.27–2.13 (m, 2H), 1.90 (m, 1H), 1.67 (m, 1H), 1.48–1.30 (m, 4H), 0.75 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.3, 138.9, 129.8, 127.8, 125.9, 106.0, 81.4, 81.3, 74.9, 42.5, 36.1, 30.1, 28.8, 28.6, 10.1; HRMS calcd for $C_{17}H_{22}O$ (M^+): 242.1671, found: 242.1679; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 6.9 min (97.7%), 8.3 min (2.3%).

4.2.14. (2R,7S)-7-Ethyl-2-phenethyl-3-vinylideneoxepane (**17e**)

Chromatography (1:99 Et_2O/hexane) afforded 45.6 mg (89%), colorless oil. $[\alpha]_D$ +166.8 (c 0.1, CH_2Cl_2); IR (neat) 2927, 1953, 1454, 1090, 846, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30–7.14 (m, 5H), 4.75–4.60 (m, 2H), 4.07 (ddd, J=9.9, 4.8, 2.1 Hz, 1H), 3.27 (ddd, J=9.8, 4.6, 1.2 Hz, 1H), 2.81 (ddd, J=15.7, 10.3, 5.6 Hz, 1H), 2.66 (ddd, J=16.1, 10.1, 6.0 Hz, 1H), 2.30–2.10 (m, 2H), 2.0 (m, 1H), 1.91 (m, 1H), 1.86–1.67 (m, 2H), 1.59–1.34 (m, 4H), 0.94 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.3, 142.4, 128.4, 128.2, 125.6, 107.2, 81.3, 79.4, 75.2, 37.9, 36.1, 32.2, 30.2, 28.8, 28.7, 10.5; HRMS calcd for $C_{18}H_{24}O$ (M^+): 256.1827, found: 256.1821; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 7.9 min (97.5%), 8.6 min (2.5%).

4.2.15. (2S,7S)-7-Ethyl-2-(furan-2-yl)-3-vinylideneoxepane (**17f**)

Chromatography (4:96 Et_2O/hexane) afforded 35.3 mg (81%), brown oil. $[\alpha]_D$ +117.8 (c 0.9, CH_2Cl_2); IR (neat) 2929, 1957, 1261, 1069, 849, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (dd, J=1.8, 0.9 Hz, 1H), 6.31 (dd, J=2.9, 1.8 Hz, 1H), 6.24 (dd, J=3.3, 0.9 Hz, 1H), 5.17 (t, J=1.8 Hz, 1H), 4.78 (ddd, J=10.3, 3.3, 1.7 Hz, 1H), 4.71 (ddd, J=10.3, 3.7, 2.0 Hz, 1H), 3.45 (m, 1H), 2.40–2.31 (m, 2H), 1.96 (m, 1H), 1.76 (m, 1H), 1.65–1.40 (m, 4H), 0.98 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.5, 154.9, 142.1, 109.9, 106.4, 105.0, 80.9, 75.9, 75.8, 35.8, 30.1, 29.1, 28.8, 10.4; HRMS calcd for $C_{14}H_{18}O_2$ (M^+): 218.1307, found: 218.1316; HPLC (DAICEL CHIRALCEL OB-H, 25 cm×0.46 cm I.D., rate 0.2 mL/min, hex/IPA=99:1) 18.3 min (98.9%), 21.4 min (1.1%).

4.2.16. (2S,7S)-2,7-Diphenyl-3-vinylideneoxepane (**18a**)

Chromatography (3:97 Et_2O/hexane) afforded 52.5 mg (95%), yellow oil. $[\alpha]_D$ −49.6 (c 0.2, CH_2Cl_2); IR (neat) 2928, 1954, 1449, 1067, 850, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51–7.25 (m, 10H), 5.38 (s, 1H), 4.87 (ddd, J=10.3, 3.1, 1.6 Hz, 1H), 4.78 (m, 1H), 4.74 (d, J=10.5 Hz, 1H), 2.29 (m, 1H), 2.18 (m, 1H), 2.06–2.01 (m, 2H), 1.84 (m, 1H), 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.1, 144.4, 142.5, 128.2, 128.0, 127.1, 126.9, 126.1, 125.6, 106.9, 80.9, 80.0, 75.8, 39.0, 29.4, 27.7; HRMS calcd for $C_{20}H_{20}ONa$ (M+Na)$^+$: 299.1406, found: 299.1418; HPLC (DAICEL CHIRALCEL OK, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 13.2 min (90.0%), 18.3 min (10.0%).

4.2.17. (2S,7S)-2-(4-Nitrophenyl)-7-phenyl-3-vinylideneoxepane (**18b**)

Chromatography (6:94 Et_2O/hexane) afforded 48.0 mg (75%), colorless oil. $[\alpha]_D$ −56.8 (c 0.2, CH_2Cl_2); IR (neat) 2932, 1954, 1519, 1346, 1096, 851, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20–8.17 (m, 2H), 7.66–7.65 (m, 2H), 7.42–7.38 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 5.44 (s, 1H), 4.94 (dd, J=10.7, 1.4 Hz, 1H), 4.84 (m, 1H), 4.76 (d, J=10.5 Hz, 1H), 2.30 (m, 1H), 2.12–2.03 (m, 3H), 1.87 (m, 1H), 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.1, 149.7, 147.1, 143.8, 128.3, 127.2, 126.8, 125.5, 123.3, 106.2, 80.6, 80.2, 76.6, 38.9, 29.1, 27.7; HRMS calcd for $C_{20}H_{19}NO_3Na$ (M+Na)$^+$: 344.1257, found: 344.1273; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 1.0 mL/min, hex/IPA=95:5) 12.2 min (8.6%), 17.0 min (91.4%).

4.2.18. (2S,7R)-7-Phenyl-2-phenethyl-3-vinylideneoxepane (**18c**)

Chromatography (3:97 Et_2O/hexane) afforded 54.0 mg (89%), colorless oil. $[\alpha]_D$ −89.2 (c 0.3, CH_2Cl_2); IR (neat) 2927, 1953, 1453, 1096, 851, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.12 (m, 10H), 4.76 (m, 1H), 4.70 (m, 1H), 4.46 (d, J=10.1 Hz, 1H), 4.22 (m, 1H), 2.80 (m, 1H), 2.68 (m, 1H), 2.35–2.30 (m, 2H), 2.10–1.95 (m, 3H), 1.87 (m, 1H), 1.74 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.5, 144.5, 142.2, 128.5, 128.4, 128.2, 128.1, 126.8, 125.6, 106.9, 81.0, 79.2, 75.5, 38.8, 37.9, 32.1, 29.2, 28.6; HRMS calcd for $C_{22}H_{24}O$ (M^+): 304.1827, found: 304.1815; HPLC (DAICEL CHIRALCEL OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=95:5) 12.4 min (92.7%), 14.6 min (7.3%).

4.2.19. (2R,6S)-6-Ethyl-2-phenyldihydro-2H-pyran-3(4H)-one (**19**)

A stirred solution of **15a** (26.0 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) at −78 °C was bubbled a stream of ozone for 5 min. The color of the solution changed from colorless to pink to blue, and the resulting solution was stirred for 20 min at −78 °C. Air was then passed through the reaction mixture until the blue color disappeared. The DMS (0.30 mmol, 23 mg) was added to the solution and the dry ice bath was removed and the reaction mixture stirred at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed on silica gel with 5% Et_2O in hexane to furnish the ketone **19** (24 mg, 97%). $[\alpha]_D$ −13.7 (c 0.3, CH_2Cl_2); IR (neat) 2966, 1726, 1452, 1275, 1097, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 5H), 4.90 (s, 1H), 3.78 (m, 1H), 2.73 (ddd, J=15.7, 7.2, 4.9 Hz, 1H), 2.52 (ddd, J=15.7, 9.3, 7.3 Hz, 1H), 2.16 (dddd, J=15.8, 7.3, 3.7, 1.3 Hz, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 1.02 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.5, 136.1, 128.2, 128.1, 127.3, 85.6, 77.5, 36.8, 30.7, 28.8, 9.9; HRMS calcd for

$C_{13}H_{16}O_2$ (M^+): 204.1150, found: 204.1155; HPLC (DAICEL CHIRALPAK AS-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=98:2) 12.9 min (98.0%), 15.7 min (2.0%).

*4.2.20. (2R,3R,6S)-6-Ethyl-2-phenyltetrahydro-2H-pyran-3-ol (**20**)*

To a stirred of **19** (20 mg, 0.10 mmol) in THF (3 mL) was added L-Selectride® (0.12 mL, 0.2 mmol, 1 M in THF) at −78 °C and the mixture was stirred for 3 h at −78 °C. The reaction was quenched with water (1 mL) at −78 °C, warmed to room temperature, extracted with Et_2O (3×5 mL), dried, and concentrated. Chromatography of the residue (silica gel, elution with 10% ethyl acetate in hexanes) delivered 12 mg (92%) of **20** as a colorless liquid. $[\alpha]_D$ −24.5 (*c* 0.5, CH_2Cl_2); IR (neat) 3444, 2937, 1451, 1068, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.24 (m, 5H), 4.55 (s, 1H), 3.94 (m, 1H), 3.46 (m, 1H), 2.12 (ddd, *J*=13.7, 6.7, 3.0 Hz, 1H), 1.86 (ddd, *J*=13.7, 4.7, 2.7 Hz, 1H), 1.69–1.50 (m, 5H), 1.00 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.8, 128.4, 127.3, 125.8, 80.7, 79.8, 67.5, 30.4, 29.2, 24.9, 9.9. HRMS calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307, found: 206.1296; HPLC (DAICEL CHIRALPAK AD-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 19.0 min (3.0%), 23.2 min (97.0%).

*4.2.21. (2R,3S,6S)-6-Ethyl-2-phenyltetrahydro-2H-pyran-3-ol (**21**)*

To a stirred of **19** (20 mg, 0.10 mmol) in Et_2O (3 mL) was added $LiAlH_4$ (0.10 mL, 0.1 mmol, 1 M in Et_2O) at −78 °C and the mixture was stirred for 3 h. The reaction was quenched with water (1 mL) at −78 °C, warmed to room temperature, extracted with Et_2O (3×5 mL), dried, and concentrated. Chromatography of the residue (silica gel, elution with 10% ethyl acetate in hexanes) delivered 11 mg (88%) of a nonseparable mixture of **21** and **20** in a ratio of 10:1, respectively. IR (neat) 3445, 2962, 1451, 1095, 697 cm^{-1}; HRMS calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307, found: 206.1304; ^1H NMR (500 MHz, $CDCl_3$) δ signals due to **21**: 7.43–7.28 (m, 5H), 4.02 (d, *J*=9.0 Hz, 1H), 3.49 (m, 1H), 3.40 (m, 1H), 2.19 (m, 1H), 1.83 (m, 1H), 1.70–1.45 (m, 4H), 1.42 (d, *J*=2.7 Hz, 1H (OH)), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.9, 128.6, 128.2, 127.5, 84.9, 79.1, 71.9, 31.9, 30.4, 28.6, 9.9; HPLC signals due to **21** (DAICEL CHIRALPAK OJ-H, 25 cm×0.46 cm I.D., rate 0.5 mL/min, hex/IPA=99:1) 12.3 min (97.0%), 20.8 min (3.0%).

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