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A New Method for the Preparation of the 6,6 and 6,7 Ring Systems of Bicyclic Ethers

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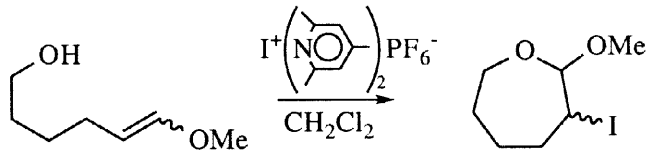
Abstract: Preparation of 2,7-dioxabicyclo[4.4.0]decane and 2,8-dioxabicyclo[5.4.0]undecane derivatives in five steps from dihydropyran are reported. Transformation of 3-bromo-2-allyloxepane into 2,7-dioxabicyclo-[5.4.0]-undecane is also described.

Keywords: Cyclization; oxepanes; halogens and compounds; enol ethers.

INTRODUCTION

An always increasing number of natural products[1] possessing polycyclic ether frameworks, such as ciguatoxins, maitotoxin or brevetoxins, have inspired numerous research groups to study original ways to synthesize them.[2,3] These efforts have recently culminated in the synthesis of some of these natural products.[4]

Preparation of tetrahydropyran derivatives by 6-*endo* electrophilic cyclizations of hydroxy-enol ethers has been reported to lead to interesting synthetic applications.[5] Preparation of oxepane derivatives by similar 7-*endo* electrophilic cyclizations does not seem to be know. However, we recently reported that this kind of cyclization could be carried out using bis(*sym*-collidine)iodine(I) hexafluorophosphate as an electrophilic reagent (scheme 1).[6] We decided to examine if the resulting 2,3-difunctionalized ethers could be transformed into bicyclic ethers with the same functionalities, thus allowing an iterative construction of polycyclic ethers (Scheme 1).



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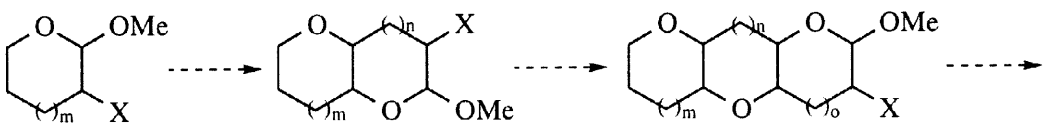

Scheme 1

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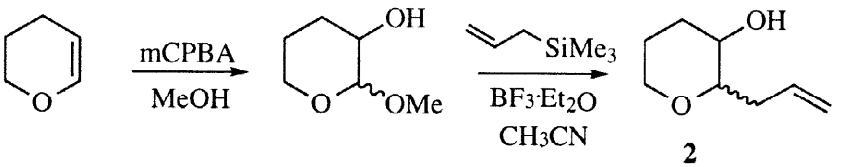
RESULTS

Preparation of 6,6 bicyclic ethers

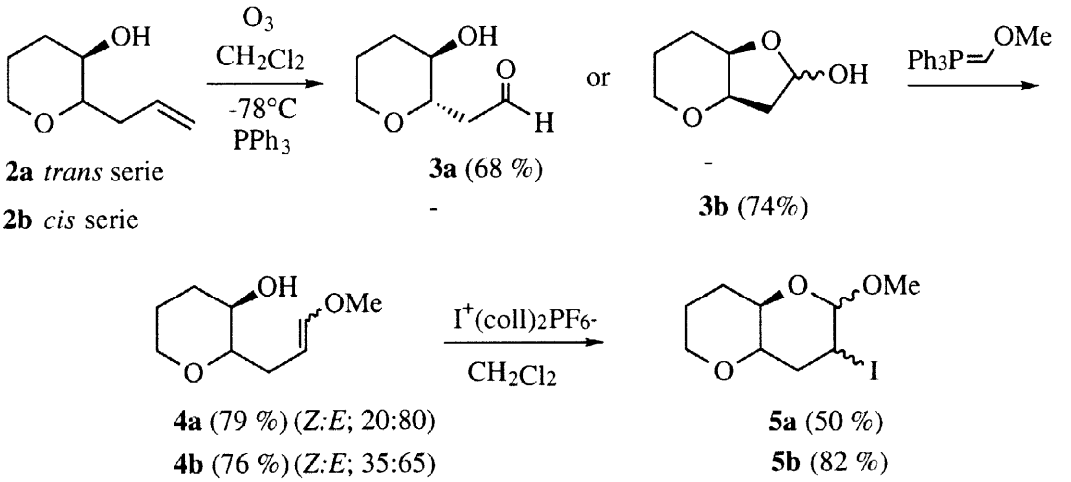
Epoxidation of dihydropyran in methanol led to 2-hydroxy-1-methoxytetrahydropyran in good yield (70%)[7] which was readily alkylated at the 2 position using allyltrimethylsilane in the presence of boron-trifluoride diethyletherate in acetonitrile (73% yield).[8] 2-Allyl-3-hydroxytetrahydropyran **2** was obtained as a 65: 35 *cis-trans* mixture of diastereoisomers (Scheme 2).



2

Scheme 2

Protection of the alcohol as the acetate or *tert*-butyldimethylsilylether before the reaction with allyltrimethylsilane did not improve the selectivity. However, the two diastereoisomers could be easily separated by liquid chromatography over silica gel and were fully characterized from their ^{1}H and ^{13}C-NMR spectra. The subsequent reactions were conducted on each pure diastereoisomer. Ozonolysis of *trans* pyran **2a** led to the hydroxyaldehyde **3a** characterized from its NMR and IR spectra. This compound reacted with methoxymethyltriphenylphosphorane to afford the enol ether **4a**, as a *Z:E* mixture (20:80). Reaction of this mixture with bis(*sym*-collidine)iodine(I) hexafluorophosphate led to the bicyclic iodo ether **5a** in moderate yield (50%) (Scheme 3), as a mixture of the four diastereoisomers (14:21:26:39), whose relative configurations could not be assigned.



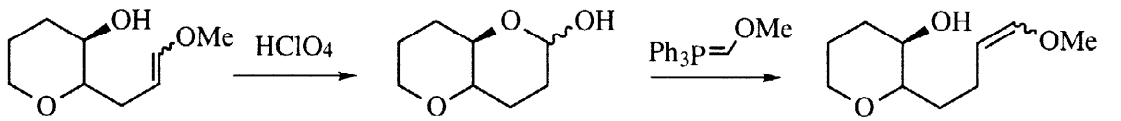
2a *trans* serie
2b *cis* serie
3a (68 %)
-
-
3b (74%)
4a (79 %) (*Z:E*; 20:80)
4b (76 %) (*Z:E*; 35:65)
5a (50 %)
5b (82 %)

Scheme 3

The same reaction sequence was conducted in the *cis* serie. In this case, the ozonolysis led to furanol **3b** which after Wittig reaction and iodoetherification led to a mixture of three diastereoisomers (15:15:70) of the bicyclic compound in good yield (82%), whose relative configurations could not be assigned (Scheme 3).

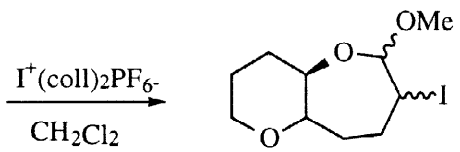
Preparation of 6,7 bicyclic ethers.

This strategy was applied to the preparation of the 6,7 bicyclo compounds. Hydrolysis of enol ether **4a** using perchloric acid led to the corresponding hemiacetal **6a** which after Wittig reaction using methoxymethyltriphenylphosphorane, was transformed into the enol ether **7a**. The iodoetherification of this latter carried out in methylene chloride in the presence of bis(*sym*-collidine)iodine(I) hexafluorophosphate giving the desired bicyclic compound **8a** in moderate yield (38%) as a mixture of three diastereoisomers (Scheme 3). These products were characterised from their NMR and mass spectra.



4a *trans* serie **6a** (80 %) **7a** (60 %) (*Z:E*; 80:20)

4b *cis* serie **6b** (89 %) **7b** (67 %) (*Z:E*; 80:20)



8a (38 %)

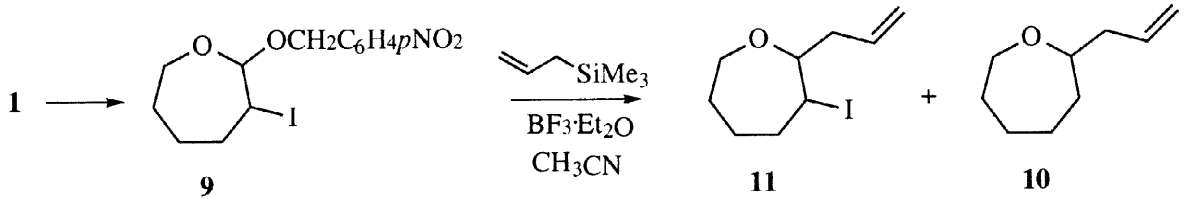
8b (81 %)

Scheme 4

The preparation of the *cis* 6,7 bicyclic compound **8b** was performed in an analogous manner starting from the enol ether **4b**. Hydrolysis, followed by the Wittig reaction and iodoetherification led to the *cis* bicyclo ether **8b** as a mixture of three diastereoisomers (Scheme 4). As in the 6,6 series, it appreared that the iodoetherification of the *cis* compound was more efficient than the *trans* series.

Preparation of 7,6 bicyclic ether.

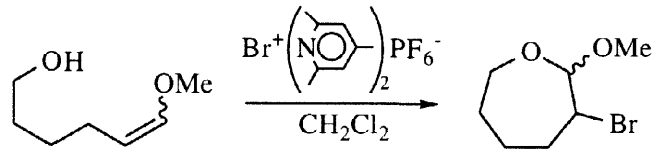
In view of the preparation of polycyclic ethers analogous to brevetoxin derivatives, we decided to test the preparation of bicyclic compounds starting from oxepane **1**. While the allylation of tetrahydropyran is well known,[8] to our knowledge nothing has been reported starting with oxepanes. Reaction of oxepane **1** with allyltrimethylsilane in the presence of Lewis acids such as $AlCl_3$, $ZnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, or $CF_3SO_2SiMe_3$ led to degradation products and (or) oxepane ring cleavage products. After reaction with 4-nitrobenzyl alcohol in the the presence of *p*-toluenesulfonic acid and a radical scavenger, the resulting acetal **9** was C-2 alkylated with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$. An inseparable mixture of 2-allyloxepane **10** and 2-allyl-3-iodooxepane **11** was obtained (Scheme 5). In the absence of the radical inhibitor, 2-allyloxepane **10** was obtained as the sole product (57%).



9 **11** **10**

Scheme 5

To avoid radical halogen removal, the more stable bromine derivative **13** was studied. This substrate was prepared by a 7-*endo* cyclization of alcohol **12** using bis(*sym*-collidine)bromine(I) hexafluorophosphate (74% yield) (Scheme 6).

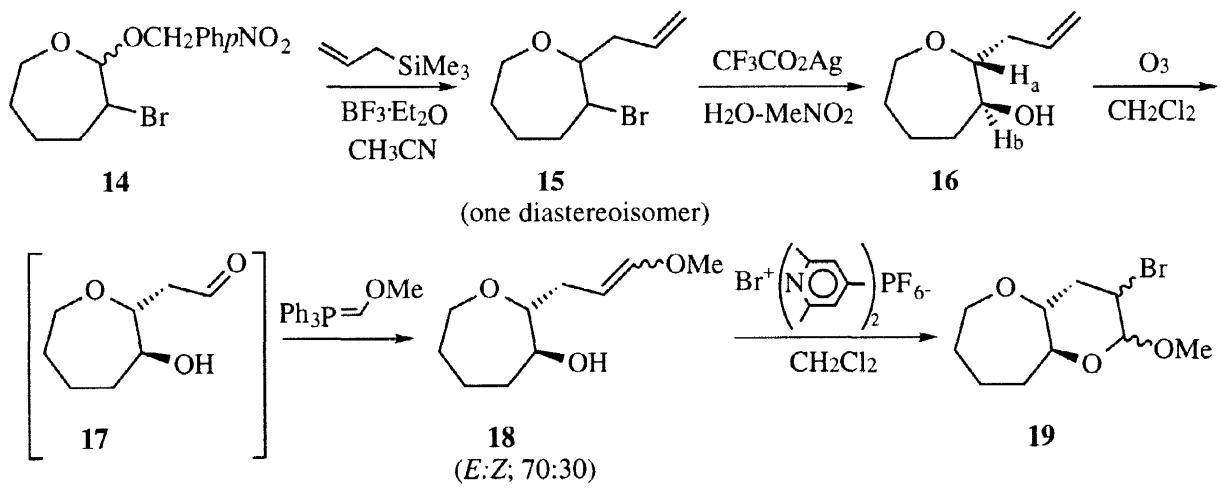


12 **13**

Scheme 6

As with the iodine derivative **1,** the transacetalization in the presence of 4-nitrobenzyl alcohol led to the desired acetal **14** which was alkylated using allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ without bromine removal (74%). Only one diastereoisomer, **15**, of unknown stereochemistry was isolated. Reaction of the bromooxepane **15** with 2 equivalents of silver trifluoroacetate in a mixture of water-nitromethane at pH 7 led to the corresponding alcohol **16** as a 97:3 mixture (87.5% yield). The stereochemistry of the main isomer was found to be *trans* by analysis of its ^{1}H-NMR spectra. Indeed, by irradiation of the CH_2 of the allyl group a coupling constant of 7 Hz was found between the two hydrogens H_a and H_b (Scheme 7). This stereochemistry was confirmed by calculation of the conformation of each diastereoisomers by molecular modelling (Pro Chemist Model 5.3 and MAD programs).

The carbon-carbon double bond of this *trans* alcohol was cleaved with ozone and the resulting hydroxyaldehyde **17** reacted with methoxymethyltriphenylphosphorane to provide the enol ether **18** (45% yield from **16**). The bromoetherification in the presence of bis(*sym*-collidine)bromine(I) hexafluorophosphate gave the desired bicyclic compound **19** (31% yield) as a mixture of three diastereoisomers (Scheme 7).



14 **15** (one diastereoisomer) **16**

17 **18** (*E*:*Z*; 70:30) **19**

Scheme 7

In conclusion, these results have shown that it is possible to prepare by haloetherification, 6,6-, 6,7- and 7,6 bicyclic ethers with *cis* or *trans* stereochemistry present in natural products such as maitotoxin. Work is now in progress to improve these transformations and to apply this reaction pathway to an iterative preparation of polycyclic ethers.

EXPERIMENTAL

^1H and ^{13}C spectra were recorded in $CDCl_3$ solution on Brucker AM 200, 250 and 50.3, 62.9 MHz, respectively. Infrared spectra were recorded on a Perkin-Elmer 682. Mass spectra were determined on a NERMAG R10 - 10 spectrometer. Flash chromatography was performed on SiO_2 (SDS 35 - 70 microns). Bis(*sym*-collidine)iodine(I) hexafluorophosphate and bis(*sym*-collidine)bromine(I) hexafluorophosphate are abbreviated as HBI and HBB respectively. HBB was prepared as reported for HBI.[6]

3-Iodo-2-methoxyoxepane 1. To 6-methoxyhex-5-en-1-ol (1 mmol) in dichloromethane (20 mL) was added HBI (1.2 equiv., 1.2 mmol, 620 mg) at rt. After half an hour, silica gel (3 g) was added and solvent was evaporated under vacuum. Purification of the product by column chromatography (ether:hexane; 5:95) gave 215 mg (0.84 mmol) of a mixture of two diastereoisomers (*cis:trans;* 35:65, 84% yield). *Trans*-diastereoisomer **1a**. ^1H NMR δ 1.35 - 1.80 (m, 4H), 2.06 - 2.37 (m, 2H), 3.37 (s, 3H), 3.54 (ddt, J = 12, 2.6, 1 Hz, 1H), 3.82 (m, 1H), 4.08 (ddd, J = 10.5, 7.8, 2.6 Hz, 1H), 4.85 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ 28.9, 29.6, 32.5, 37.4, 55.6, 63.2, 109.5. MS EI (*m/z*, %): 61(81), 69 (100), 97 (37), 129 (37), 154 (30). *Cis*-diastereoisomer **1b**. ^1H NMR δ 1.47 - 1.95 (m, 4H), 2.02-2.35 (m, 2H), 3.45 (s, 3H), 3.72 (m, 1H), 3.94 (m, 1H), 4.19 (d, J = 2 Hz, 1H), 4.33 (ddd, J = 5.2, 4.2, 1 Hz, 1H). ^{13}C NMR δ 24.7, 29.5, 31.8, 35.8, 55.9, 64.8, 103.3. MS EI (*m/z*, %): 61(100), 69 (86), 71(34), 97 (28), 129 (26), 154 (23).

2-Allyl-3-hydroxytetrahydropyran 2. To a solution of 3-hydroxy-2-methoxytetrahydropyran (50.7 mmol) in acetonitrile (530 mL), under argon were added at 0°C, allyltrimethylsilane (2.5 equiv., 127 mmol, 20 mL), and boron trifluoride diethyletherate (2.5 equiv., 127 mmol, 16 mL). The solution was allowed to warm to rt and stirred for 3 h. Saturated aqueous sodium hydrogen carbonate was added and the organic layer extracted with ether. The combined organic extracts were dried (Na_2SO_4), concentrated and purified by flash silica gel column chromatography (ether:hexane; 60:40). A mixture of two diastereoisomers partially separated was obtained (5.2 g, *cis:trans*; 65:35, 73% yield). *Trans*-diastereoisomer **2a**.[9] ^1H NMR δ 1.44 - 1.6 (m, 2H), 1.60 (s, 1H, OH), 1.68 (m, 1H), 2.11 (m, 1H), 2.30 (m, 1H), 2.60 (m, 1H), 3.12 (td, J = 7.5, 4 Hz, 1H), 3.28 - 3.43 (m, 2H), 3.92 (m, 1H), 5.13 (m, 2H), 5.94 (m, 1H). *Cis*-diastereoisomer **2b**.[9] ^1H NMR δ 1.30 - 2.04 (m, 4H), 2.32 (m, 2H), 3.37 (m, 1H), 3.70 (m, 2H), 4.00 (m, 1H), 5.11 (m, 2H), 5.80 (m, 1H), 8.02 (s, 1H, OH). MS EI (*m/z*, %): 41(30), 43 (54), 44 (49), 55 (17), 57 (16), 71 (21), 101 (100), 142 (1). IR (film) (cm^{-1}): 3440, 3080, 2950, 2860, 1650, 1440, 1100, 1000.

Ozonolysis of olefins 2a and 2b. Ozone-oxygen gas was bubbled into a solution of 2-allyl-3-hydroxytetrahydropyran **2** (10.5 mmol,1.5 g) in a 4:1 dichloromethane-methanol mixture (70 mL) cooled at -78°C, until a persistent blue color appeared. The solution was stirred for 30 min at -78°C and argon was bubbled into the solution to eliminate the excess ozone. Triphenylphosphine (15.75 mmol, 4.15 g, 1.5 equiv.) was added and the mixture was allowed to warm to rt. The solution was concentrated under vacuum and the crude product purified by silica gel column chromatography (ether:hexane; 60:40) to give 8-hydroxy-2,7-dioxabicyclo(4.3.0)nonane **3b** (1.15 g, 76% yield) from *cis*-isomer **2b** and 2-(2-oxoethyl)-3-hydroxytetrahydropyran **3a** (1.03 g, 68% yield) from *trans*-isomer **2a**. (2S*,3R*)-2-(2-oxoethyl)-3-hydroxytetrahydropyran **3a**. ^1H NMR δ 1.32 - 2.24 (m, 4H), 2.31 - 2.45 (s, 1H, OH), 2.55 (ddd, J = 16, 8, 2 Hz, 1H), 2.90 (ddd, J = 16, 5, 2 Hz, 1H), 3.26 - 3.45 (m, 2H), 3.60 (ddd, J = 7.5, 5.3, 3.3 Hz, 1H), 3.88 (m, 1H), 9.77 (t, J = 2 Hz, 1H). ^{13}C NMR δ 25.3, 32.8, 46.7, 67.6, 69.8, 77.6, 201.9. Anal. Calcd for $C_7H_{12}O_3$: C, 58.30 ; H, 8.39. Found: C, 58.40; H, 8.18. (1R*,6R*)-8-hydroxy-2,7-dioxabicyclo[4.3.0]nonane **3b**. ^1H NMR δ 1.32 - 1.54 (m, 1H), 1.63 - 1.82 (m, 2H), 1.85 - 2.12 (ddt, J = 15, 4.2, 5 Hz, 2H), 2.09 - 2.23 (m, 1H), 2.30 (dd, J = 15, 5 Hz, 0.6H, OH α isomer), 2.95 (d, J = 3.4 Hz, 0.4H, OH β isomer), 3.27 - 3.44 (ddt, J = 2, 12 Hz, 1H), 3.85 (m, 1H), 3.92 - 4.15 (m, 2H), 5.35 (dt, J = 3.4, 12.7 Hz, 0.4H, β isomer), 5.75 (dt, J = 3.4, 5 Hz, 0.6H, α isomer). ^{13}C NMR δ α isomer: 20.1, 25.6, 42.0, 66.8, 75.8, 76.7, 99.1. β isomer : 20.1, 25.6, 42.8, 66.4, 74.2, 77.0, 98.4. MS EI (*m/z*, %): 41 (34), 42 (22), 43 (56), 44 (37), 45 (21), 55 (31), 56 (27), 57 (37), 71

(100), 73 (30), 80 (20), 83 (23), 84 (18), 98 (20), 126 (21), 144 (2). IR (film) (cm^{-1}): 3420, 2960, 2860, 1450, 1240, 1130, 1100, 1060, 1020. Anal. Calcd for $C_7H_{12}O_3$: C, 58.30 ; H, 8.39. Found: C, 58.47; H, 8.12.

3-Hydroxy-2-(3-methoxyprop-2-enyl)tetrahydropyran 4. To a mixture of methoxymethyltriphenylphosphonium chloride (20.8 mmol, 7.15 g, 3 equiv.) and anhydrous THF (52 mL) under argon atmosphere at -78°C, was added dropwise *tert*butyllithium (20.8 mmol, 13.9 mL of a 1.5 M soln. in pentane, 3 equiv.). After 10 min. of stirring, a solution of lactol **3a** (or aldehyde **3b**) (6.9 mmol) in THF (10 mL) was added. The mixture was allowed to warm to rt and stirred for 15 h. The reaction was quenched by addition of water (10 mL). The solvent was evaporated under vacuum and the aqueous layer extracted with methylene chloride. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (ether:hexane; 80:20) to obtain a mixture of two isomers (*Z:E*; 45:55, 725 mg, 73% yield for **4a**), (*Z:E*; 35:65, 937 mg, 79% yield for **4b**). (2S*,3R*)-3-Hydroxy-2-(3-methoxyprop-2-enyl)tetrahydropyran **4a**. ^1H NMR δ 1.32 - 2.13 (m, 4H), 2.16 (t, J = 6.8 Hz, 0.8H, OH), 2.25 - 2.70 (m, 2H), 2.94 (m, 0.2H, OH), 2.95 - 3.2 (m, 1H), 3.25 - 3.45 (m, 2H), 3.53 (s, 2.4H, OMe), 3.62 (s, 0.6H, OMe), 3.80 - 3.85 (m, 1H), 4.53 (dt, J = 8.4, 6.3 Hz, 0.2H), 4.82 (dt, J = 12.6, 7.3 Hz, 0.8H), 6.03 (d, J = 6.3 Hz, 0.2H), 6.38 (d, J = 12.6 Hz, 0.8H). ^{13}C NMR δ *E*-isomer : 25.4, 30.2, 32.6, 55.6, 67.4, 69.4, 82.4, 98.3, 148.1. *Z*-isomer : 25.5, 26.1, 31.4, 59.4, 67.6, 68.9, 82, 101.9, 147.4. Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.37. Found: C, 62.86; H, 9.35. (2R*,3R*)-3-Hydroxy-2-(3-methoxyprop-2-enyl)tetrahydropyran **4b**. ^1H NMR δ 1.25 -1 .45 (m, 1H), 1.50 - 1.17 (m, 1H), 1.78 - 2.20 (m, 2H), 2.10 - 2.48 (m, 2H+OH *E*-isomer), 2.68 (d, J = 6.8 Hz, 0.65H, OH *Z*-isomer), 3.15 - 3.3 (m, 2H), 3.46 (dt, J = 11, 1 Hz, 1H), 3.49 (s, 1.95H, OMe *E*-isomer), 3.59 (s, 1.05H, OMe *Z*-isomer), 3.60 - 3.71 (m, 1H), 3.9 - 4.1 (m, 1H), 4.38 (dt, J = 9.5, 5.8 Hz, 0.35H), 4.69 (dt, J = 7.3, 13.2 Hz, 0.65H), 5.98 (d, J = 5.8 Hz, 0.35H), 6.35 (d, J = 13.2 Hz, 0.65H). ^{13}C NMR δ *E*-isomer : 20.0, 29.9, 30.5, 55.8, 65.4, 68.5, 80.5, 98.0, 148.7. *Z*-isomer : 20.1, 26.3, 30.0, 59.5, 65.2, 68.4, 79.0, 101.6, 147.9. MS EI (*m/z*, %): 41 (39), 43 (82), 55 (44), 59 (19), 69 (15), 71 (74), 72 (25), 83 (29), 84 (16), 100 (14), 101 (100). IR (film) (cm^{-1}): 3450, 3060, 2960, 2860, 1660, 1450, 1220, 1090, 1000. Anal. Calcd for $C_9H_{16}O_3$: C, 62.75 ; H, 9.37. Found: C, 62.80; H, 9.30.

4-Iodo-3-methoxy-2,7-dioxabicyclo[4.4.0]decane 5. To a mixture of enol ether **4a** (or **4b**) (2.9 mmol, 500 mg) in methylene chloride (60 mL), HBI (3.5 mmol, 1.79 g, 1.2 equiv.) was added at room temperature. The mixture was stirred for 15 min. Silica gel (500 mg) was added to the solution and the solvent removed under vacuum. Purification by chromatography on silica gel column (ether:hexane; 30:70) led to a mixture of three diastereoisomers (15:15:70) from which only one isomer could be separated for compound **5b** (2.4 mmol, 82% yield) and to four partially separable diastereoisomers (14:21:26:39) of compound **5a** (1.5 mmol, 50% yield). (1R*, 6S*)-4-iodo-3-methoxy-2,7-dioxabicyclo[4.4.0]decane **5a**, 2 isomers, C8-C9 *trans:cis*; 90:10. ^1H NMR δ 1.43 - 1.8 (m, 3H), 2.00 - 2.11 (m, 1H), 2.11 (dt, J = 12.8, 11.2 Hz, 1H), 2.27 - 2.40 (m, 0.2H), 2.63 (dt, J = 12.6, 4.5 Hz, 1H), 2.96 (ddd, J = 10.8, 8.4, 4.5 Hz, 1H), 3.17 (ddd, J = 8.9, 8.4, 4.2 Hz, 1H), 3.28 - 3.40 (m, 1H), 3.41 (s, 0.3H, OMe *cis*-isomer), 3.50 (2.7H, OMe *trans*-isomer), 3.85 - 4.00 (m, 1.9H), 4.05 - 4.15 (m, 0.1H), 4.43 (d, J = 8.8 Hz, 1H), 4.63 (d, J = 3.9 Hz, 0.1H). ^{13}C NMR δ 21.4/24.03, 24.95/25.46, 28.9/29.0, 36.9/41.9, 55.5/57.3, 67.0/67.8, 68.2/75.6, 77.7/78.3, 99.1/105.6. 2 isomers, C8-C9 *trans:cis*; 35:65. ^1H NMR δ 1.30 - 1.84 (m, 3H), 1.88 - 2.40 (m, 1H), 2.04 - 2.15 (m, 1.3H), 2.25 - 2.40 (m, 0.7H), 3.00 (ddd, J = 9.9, 7.9, 5.9 Hz, 0.35H), 3.29 - 3.60 (m, 2.65H), 3.50 (s, 1.95H, OMe *cis*-isomer), 3.41 (s, 1.05H, OMe *trans*-isomer), 3.83 - 3.97 (m, 1H), 4.04 - 4.15 (m, 0.35H), 4.34 (t, J = 2.9 Hz, 0.65H), 4.63 (d, J = 3.9 Hz, 0.35H), 4.85 (s, 0.65H). ^{13}C NMR δ 21.4/25.8, 25.5/26.2, 28.8/28.9, 33.8/37.0, 54.6/55.5, 67.9/68.1, 68.2/69.7, 75.1/78.3, 99.1/101.5. Anal. Calcd for $C_9H_{15}O_3I$: C, 36.24; H, 5.07. Found: C, 36.23; H, 5.10. (1R*,6R*)-4-iodo-3-methoxy-2,7-dioxabicyclo[4.4.0]decane **5b**, 2 isomers, C3-C4 *trans:cis*; 50:50. ^1H NMR δ 1.15 - 1.43 (m, 1H), 1.55 - 1.78 (m, 1H), 1.86 - 2.09 (m, 2H), 2.14 - 2.31 (m, 1H), 2.49 - 2.65 (m, 1H), 3.15 - 3.22 (m, 0.5H), 3.29 - 3.48 (m, 1H), 3.36 (s, 1.5H), 3.50 (s; 1.5H), 3.53 - 3.68 (m, 1H), 3.75 - 3.82 (m, 0.5H), 3.88 - 4.10 (m, 1.5H), 4.11 - 4.28 (m, 0.5H), 4.40 (d, J = 7.9 Hz, 0.5H), 5.05 (s, 0.5H). ^{13}C NMR δ 16.7/20.1,

20.5/25.0, 28.0/28.1, 32.7/42.7, 54.7/56.5, 62.5/67.8, 67.4/71.3, 70.2/74.0, 103.1/105.5. 1 isomer. ^{1}H NMR δ 1.30 (dq, J = 13 Hz, 1H), 1.62 (ddd, J = 14.4, 4.9, 3.9 Hz, 1H), 1.76 - 2.05 (m, 2H), 2.24 (dt, J = 13.6, 3.5 Hz, 1H), 2.50 (td, J = 3.2, 13.4 Hz, 1H), 3.30 (t, J = 2.9 Hz, 1H), 3.40 (s, 3H), 3.40 (td, J = 11.8, 1.9 Hz, 1H), 3.80 (s, 1H), 3.97 (m, 1H), 4.49 (ddd, J = 13.1, 4.6, 3 Hz, 1H), 4.72 (d, J = 3 Hz, 1H). ^{13}C NMR δ 20.2, 22.4, 27.9, 36.9, 55.6, 62.4, 67.8, 74.4, 99.9. MS EI (*m/z*, %): 41 (42), 43 (29), 55 (75), 71 (100), 84 (31), 111 (27), 139 (15), 140 (16), 171 (42), 298 (3). IR (film) (cm^{-1}): 2960, 2930, 2850, 1450, 1150, 1130, 1070, 1030. Anal. Calcd for $C_9H_{15}O_3I$: C, 32.26; H, 5.07. Found: C, 32.49 ; H, 5.11.

3-Hydroxy-2,7-dioxabicyclo[4.4.0]decane 6. To a solution of enol ether **4a** (or **4b**) (2.9 mmol) in THF (10 mL) was added at rt, 5 mL of a 70% aqueous perchloric acid solution. The mixture was stirred for 1 h. The reaction was quenched by addition of a saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. Chromatography of the crude product on a silica gel column (ether:hexane; 80:20) gave a mixture of two isomers (α:β; 50:50) which were not separated. (320 mg, 70% yield for **6a** from **4a**) (407 mg, 89% yield for **6b** from **4b**). (1R*,6S*)-3-hydroxy-2,7-dioxabicyclo[4.4.0]decane **6a**, 2 isomers α:β; 50:50. ^{1}H NMR δ 1.22 - 2.15 (m, 6H), 3.00 (m, 1H, OH), 3.14 (ddd, J = 4.7, 10.5, 8.5 Hz, 0.5H), 3.20 - 3.52 (m, 1.5H), 3.68 (m, 1H), 3.9 (m, 1.5H), 4.34 (m, 0.5H), 4.8 (m, 0.5H), 5.20 (s, 0.5H). ^{13}C NMR δ 23.8/25.2, 25.5/25.7, 27.9/29.7, 29.2/32.1, 67.8/67.8, 69.1/75.2, 77.4/78.3, 90.9/95.9. (1R*,6R*)-3-hydroxy-2,7-dioxabicyclo[4.4.0]decane **6b**, 2 isomers α:β; 50:50. ^{1}H NMR δ 1.20 - 2.20 (m, 8H), 3.26 (s, 0.5H, OH), 3.30 - 3.56 (m, 2H), 3.83 (m, 0.5H, OH), 3.91 - 4.45 (m, 2H), 4.74 (m, 0.5H), 5.34 (s, 0.5H). ^{13}C NMR δ 20.2/20.3, 23.1/23.9, 27.5/28.1, 28.4/28.6, 63/67.8, 67.9/70.7, 70.9/71.5, 91.7/96.4. MS EI (*m/z*, %): 41 (15), 43 (25), 55 (15), 56 (15), 57 (12), 71 (100), 84 (10), 112 (11), 140 (7), 158 (5). IR (film) (cm^{-1}): 3400, 2950, 2860, 1450, 1340, 1270, 1240, 1200, 1140, 1120, 1100, 1050, 1010, 900.

3-Hydroxy-2-(4-methoxybut-5-enyl)tetrahydropyran 7. The reaction conditions were the same as for the preparation of compound **4a** and **4b**. From lactol **6a** (or **6b**) (1.58 mmol), after purification by silica gel column chromatography (ether: hexane; 80: 20), we obtained enol ether **7a** (130 mg, 52% yield from **6a**) and enol ether **7b** (197 mg, 67% yield from **6b**) as a mixture of two isomers (*E:Z*; 80:20) not separated. (2S*,3R*)-3-hydroxy-2-(4-methoxybut-5-enyl)tetrahydropyran **7a**. ^{1}H NMR δ 1.25 - 2.2 (m, 8H), 2.33 (s, 1H, OH), 2.98 (td, J = 9.5, 2.6 Hz, 1H), 3.26 (m, 2H), 3.47 (s, 2.4H, OMe), 3.54 (s, 0.6H, OMe), 3.85 (m, 1H), 4.34 (td, J = 6.3, 6.8 Hz, 0.2H), 4.70 (dt, J = 12.6, 7.3 Hz, 0.8H), 5.84 (d, J = 6.3 Hz, 0.2H), 6.28 (d, J = 12.6 Hz, 0.8H). ^{13}C NMR δ *E*-isomer 23.4, 25.5, 32.8, 33.0, 55.7, 67.3, 70.2, 81.4, 102.6, 147.1. *Z*-isomer 19.7, 25.3, 32.0, 32.7, 59.3, 67.5, 70.1, 81.8, 106.5, 146.1. (2R*,3R*)-3-hydroxy-2-(4-methoxybut-5-enyl)-tetrahydropyran **7b**. ^{1}H NMR δ 1.30 - 2.23 (m, 9H), 3.29 (dd, J = 10.5, 6.8 Hz, 1H), 3.40 (dd, J = 15.2, 3.7 Hz, 1H), 3.50 (s, 2.4H, OMe), 3.58 (s, 0.6H, OMe), 3.62 (m, 1H), 3.97 (m, 1H), 4.44 (q, J = 7.9 Hz, 0.2H), 4.70 (dt, J = 15.8, 9.5 Hz, 0.8H), 5.87 (d, J = 7.9 Hz, 0.2H), 6.40 (d, J = 15.8 Hz, 0.8H). ^{13}C NMR δ *E*-isomer 20.2, 23.5, 30.6, 32.7, 55.8, 66.6, 68.4, 79, 102.2, 147.3. *Z*-isomer 19.8, 24.7, 27.2, 31.6, 59.4, 66.3, 67.2, 75.9, 101.3, 146.4. MS EI (*m/z*, %): 41 (32), 43 (27), 44 (25), 55 (19), 58 (23), 71 (100), 72 (17), 84 (50), 85 (19), 97 (20), 98 (26), 186 (3). IR (film) (cm^{-1}): 3440, 3020, 2950, 2860, 1660, 1450, 1210, 1160, 1130, 1100, 1060, 1000, 940. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.47; H, 9.75. Found: C, 64.50; H, 9.76.

Cyclization of enols ethers 7 with HBI. The reaction conditions were the same as for the preparation of compound **5a** and **5b**. From enol ether **7a** (or **7b**) (0.54 mmol) and after purification by silica gel column chromatography (ether:hexane; 10:90), we obtained (1R*,7S*)-4-iodo-3-methoxy-2,8-dioxabicyclo[5.4.0]-undecane **8a** (64 mg, 38% yield from **7a**) as a mixture of three diastereoisomers partially separated and (1R*,7R*)-4-iodo-3-methoxy-2,8-dioxabicyclo[5.4.0]undecane **8b** (137 mg, 81% yield from **7b**) as a mixture of three inseparable diastereoisomers. (1R*,7S*)-4-iodo-3-methoxy-2,8-dioxabicyclo[5.4.0]undecane **8a**, C3-C4 *trans*-isomer. ^{1}H NMR δ 1.30 - 2.30 (m, 8H), 3.07 (dt, J = 5.5, 9.5 Hz, 1H), 3.3 (dt, J = 5.5, 10.5 Hz, 1H), 3.41 (s, 3H, OMe), 3.46 (m, 1H), 3.84 (m, 1H), 4.00 (ddd, J = 8.9, 6.3, 0.5 Hz, 1H), 4.90 (d, J = 8.9 Hz,1H).

^{13}C NMR δ 25.3 30.4, 31.1, 33.4, 37.1, 56.2, 67.2, 68.7, 79.5, 108.4. C3-C4 (*cis:trans*; 50:50) isomers ^{1}H NMR δ 0.82 - 2.34 (m, 8H), 3.00 - 3.42 (m, 3H), 3.44 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.77 - 3.97 (m, 1.5H), 4.33 (m, 0.5H), 4.4 (s, 0.5H), 4.80 (d, J = 7.4 Hz, 1H). ^{13}C NMR δ 25.5/25.7, 29.5/29.6, 30.6/31.3, 32.7/34.0, 34.3/34.7, 56.1/56.6, 67.5/67.9, 67.9/68.0, 80.4/82.4, 100.3/112.9. Anal. Calcd for $C_{10}H_{17}O_3I$: C, 38.48 ; H, 5.49. Found: C, 38.60; H, 5.52. (1R*,7R*)-4-iodo-3-methoxy-2,8-dioxabicyclo[5.4.0]undecane **8b**, 3 isomers. ^{1}H NMR δ 1.27 - 2.17 (m, 7H), 2.40- 2.76 (m, 1H), 3.34 (s, 1.38H, OMe), 3.35 (s, 1.32H, OMe), 3.44 (s, 0.6H, OMe), 3.30 - 3.60 (m, 3H), 3.84 - 4.05 (m, 1.54H), 4.25 (td, J = 6.3, 4.73 Hz, 0.46H), 4.64 (d, J = 8.9 Hz, 0.44H), 4.69 (d, J = 3.2 Hz, 0.1H), 5.01 (d, J = 6.3 Hz, 0.46H). ^{13}C NMR δ 20.3/20.7/20.9, 29.0/29.5/29.6, 29.7/29.9/30, 30.5/32.4/33.3, 34.4/36/37, 56.2/56.6/56.4, 64.91/64.93/66.6, 67.6/67.9/68.5, 75.7/75.9/76, 101.1/108.3/112.5. MS EI (*m/z*, %): 41 (52), 42 (12), 43 (33), 55 (21), 58 (10), 71 (100), 72 (24), 97 (25), 98 (20), 125 (17); 153 (10), 185 (37), 252 (23), 312 (3). IR (film) (cm^{-1}): 2950, 2840, 1460, 1450, 1380, 1340, 1270, 1250, 1200, 1120, 1090, 1050, 1030, 960, 920, 900. Anal. Calcd for $C_{10}H_{17}O_3I$: C, 38.48; H, 5.49. Found: C, 38.62; H, 5.53.

2-(4-Nitrobenzyloxy-5-iodooxepane 9. In a round bottom flask equipped with a reflux condenser were placed compound **1** (115 mg, 0.45 mmol), 4-nitrobenzylic alcohol (1.5 equiv., 105.1 mg, 0.67 mmol), cyclohexane (25 mL), ether (4 mL), 3-*tert*butyl-4-hydroxy-5-methylphenyl sulfide (0.2 equiv., 32.3 mg, 0.09 mmol), *p*-toluenesulfonic acid (0.25 equiv., 21.4 mg, 0.11 mmol). The mixture was stirred at reflux for 48 h. The organic layer was washed with a 0.1 M aqueous solution of sodium hydroxide and then with water, dried (sodium sulfate) and concentrated under vacuum. The crude product was purified by silica gel column chromatography (ether:pentane; 10:90) to give one isomer of product **9** (103 mg, 60% yield). ^{1}H NMR δ 1.40 - 1.90 (m, 4H), 2.10 - 2.45 (m, 2H), 3.45 - 3.60 (m, 1H), 3.85 (ddd, J = 12.3 , 9 , 4.5 Hz, 1H), 4.20 (ddd, J = 11.2, 9, 3 Hz, 1H), 4.62 (d, J = 13.5 Hz, 1H), 4.84 (d, J = 13.5 Hz, 1H), 5.02 (d, J = 8 Hz, 1H), 7.58 (d, J = 9 Hz, 2H), 8.24 (d, J = 9 Hz, 2H). MS (DCI, NH_3) (*m/z*, %): 106 (100), 132 (16), 151 (13), 190 (12), 225 (22), 242 (41), 250 (11).

2-(Pro-2-enyl)oxepane 10.[10] ^{1}H NMR δ 1.40 - 1.88 (m, 8H), 2.23 (m, 2H), 3.45 - 3.62 (m, 2H), 3.86 (dt, J = 11.8, 5.3 Hz, 1H), 5.00 - 5.14 (m, 2H), 5.85 (m, 1H). MS (DCI^+, NH_3) (*m/z*, %): 141 (100), 158 (54).

3-Iodo-2-(prop-2-enyl)oxepane 11. This product was always obtained as a mixture with compound **10**.^{1}H NMR δ 1.65 - 1.80 (m, 4H), 2.20 - 2.45 (m, 3H), 2.67 - 2.80 (m, 1H), 3.40 - 3.55 (m, 1H), 3.70 - 3.82 (m, 1H), 4.07 - 4.25 (m, 2H), 4.98 - 5.20 (m, 2H), 5.72 - 5.97 (m, 1H). MS EI (*m/z*, %): 41 (100), 69 (51), 85 (40), 98 (37), 139 (39), 225 (28).

3-Bromo-2-methoxyoxepane 13. The reaction conditions were similar to those used in the preparation of 3-iodo-2-methoxy oxepane **1** with HBB in place of HBI. Product **13** was obtained as a mixture of two diastereoisomers (70:30, 74% yield). ^{1}H NMR δ 1.45 - 2.30 (m, 6H), 3.42 (s, 2.19H, OMe, *trans*-isomer), 3.49 (s, 0.81H, OMe, *cis*-isomer), 3.50 - 4.05 (m, 2.73H), 4.20 (ddd, 0.27H, *cis*-isomer), 4.63 (d, J = 1.9 Hz, 0.27H, *cis*-isomer), 4.70 (d, J = 7.2 Hz, 0.73H, *trans*-isomer). ^{13}C NMR δ (*cis-trans* mixture) 15.2, 22.8, 26.9, 29.46, 29.7, 33.8, 35.4, 54.5, 54.6, 55.6, 56.1, 63.9, 103.0, 108.1. MS EI (*m/z*, %): 41 (32.58), 61 (100), 69 (49). IR (film) (cm^{-1}): 2940, 1450, 1350, 1255, 1120, 1060.

3-Bromo-2-(4-nitrobenzyloxy)oxepane 14. In a round bottom flask with a reflux condenser were placed compound **13** (4.3 mmol, 894 mg), 4-nitrobenzylic alcohol (5.2 mmol, 786 mg), toluene (100 mL) and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at reflux for one night. The organic layer was then washed with a 0.1 M aqueous solution of sodium hydroxide and water, dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (ether:pentane; 15:95 to 10:90) to lead to product **14** (3.85 mmol, 89.5% yield) as a mixture of two diastereoisomers (*trans:cis*; 85:15). *Trans*-isomer **14**. ^{1}H NMR δ 1.40 - 1.78 (m, 3H), 1.78 - 1.96 (m, 1H), 2.05 - 2.32 (m, 2H), 3.56 (ddd, J = 9.8, 8.4, 4.2 Hz, 1H), 3.87 (ddd, J = 11.2, 8.4, 4.2 Hz, 1H), 4.08 (ddd, J = 9.8, 6.8, 2.8 Hz, 1H), 4.66 (d, J = 13.5 Hz, 1H), 4.85 (d , J = 13.5 Hz, 1H), 4.89 (d, J = 6.8 Hz, 1H), 7.58 (d, J

= 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H). ^{13}C NMR δ 27.0, 29.6, 35.4, 54.1, 64.2, 68.3, 106.5, 123.5, 128.0, 145.2, 147.3. *Cis*-isomer **14**. ^{1}H NMR δ 1.50 - 2.00 (m, 4H), 2.05 - 2.22 (m, 1H), 2.22 - 2.40 (m, 1H), 3.70 (ddd, J = 11.2, 5.6, 4.2 Hz, 1H), 4.97 (ddd, J = 12.6, 8.4, 5.6 Hz, 1H); 4.25 (ddd, J = 8.4, 4, 1.4 Hz, 1H), 4.69 (d, J = 13.5 Hz, 1H), 4.85 (d, J = 1.4 Hz, 1H), 4.94 (d, J = 13.5 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H). ^{13}C NMR δ 22.8, 29.1, 33.4, 54.2, 64.8, 68.2, 101.1, 123.3, 127.6, 145.1, 147.1. MS EI (*m/z*, %): 55 (30), 67 (40), 78 (39), 89 (47), 107 (23), 137 (100), 182 (32), 331 (0.57). IR (film) (cm^{-1}): 2940, 2870, 1610, 1530, 1350, 1110, 1060. Anal. Calcd. for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88. Found: C, 47.37; H, 4.75.

3-Bromo-2-(prop-2-enyl)oxepane 15. To a solution of compound **14** (2.66 mmol, 878.6 mg) in acetonitrile (6 mL) cooled at 0°C, under argon, were added allyltrimethylsilane (2.5 equiv., 6.65 mmol, 1.1 mL), $BF_3.Et_3O$ (2.5 equiv., 6.65 mmol, 0.82 mL). After stirring at rt for one night, a saturated solution of sodium hydrogen carbonate was added. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried (sodium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (ether:pentane; 10:90) to lead to product **15** (429 mg, 74% yield) as the sole isomer. ^{1}H NMR δ 1.60 - 1.90 (m, 4H), 2.08 - 2.40 (m, 2H), 2.60 - 2.75 (m, 2H), 3.40 - 3.55 (m, 1H), 3.64 (ddd, J = 9, 9, 3.9 Hz, 1H), 4.00 - 4.20 (m, 2H), 5.05 - 5.20 (m, 2H), 5.78 - 6.00 (m, 1H). ^{13}C NMR δ 22.6, 30.5, 37.1, 38.5, 57.4, 72.8, 86.3, 117.3, 134.5. MS EI (*m/z*, %): 41 (100), 69 (77), 79 (20), 97 (13), 179 (40), 219 (0.19). Anal. Calcd. for $C_9H_{15}BrO$: C, 49.53; H, 6.93. Found: C, 49.67; H, 7.00.

3-Hydroxy-2-(prop-2-enyl)oxepane 16. Compound **15** (1.54 mmol, 337.5 mg) was placed in a round bottom flask with nitromethane (17 mL) and phosphate buffer pH 7 (8 mL). The solution was cooled at 0°C. After addition of silver trifluoroacetate (2 equiv., 3.08 mmol, 680 mg), the reaction mixture was stirred at rt for one night, and then filtered. Azeotropic removal of solvent using acetone was pursued before purification by flash chromatography on silica gel (ether:pentane; 1:1). The allylic alcohol **16** was obtained as a mixture of two diastereoisomers (*trans:cis*; 97:3, measured by GC analysis) (210.2 mg, 87.5% yield). *Trans*-isomer **16**. ^{1}H NMR δ 1.45 - 2.05 (m, 7H), 2.20 - 2.39 (m, 1H), 2.42 - 2.55 (m, 1H), 3.28 (ddd, J = 7.9, 7.9, 3.9 Hz, 1H), 3.45 - 3.60 (m, 1H), 3.60 - 3 .72 (m, 1H), 3.95 - 4.10 (m, 1H), 5.05 - 5.20 (m, 2H), 5.85 - 6.05 (m, 1H). ^{13}C NMR δ 20.4, 30.5, 35.8, 38.5, 71.2, 75.0, 84.6, 116.7, 135.3. MS EI (*m/z*, %): 41 (36), 57 (100), 71 (14), 84 (15), 115 (27), 156 (0.06). IR (film) (cm^{-1}): 3620, 2940, 2870, 1645, 1605, 1445, 1110. Anal. Calcd. for $C_9H_{16}O_2$: C, 69.18; H, 10.33. Found: C, 69.35; H, 10.47.

Ozonolyis of compound 16. The reaction conditions applied to the preparation of the allylic alcohol **16** (1.35 mmol, 210 mg) were those used for preparation of compounds **3a** and **3b**. The crude product **17** was used for the next reaction without purification.

3-Hydroxy-2-(3-methoxyprop-2-enyl)oxepane 18. To a solution of methoxymethyltriphenylphosphonium chloride (3 equiv., 4.05 mmol, 1.38 g) in dry THF (6 mL) under argon at -78°C, was added phenyllithium (3 equiv., 4.05 mmol, 2 mL of 2 M solution in ether). The solution was stirred for 15 min. at -78°C and then the crude product **17** was added in solution in THF (3 mL). The flask was slowly warmed to rt and then stirred 24 h at this temperature. Water and dichloromethane were added and aqueous layer was extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Purification of the crude product by flash chromatography (ether:pentane; 30:70) gave compound **18** (113 mg, 45% yield from **16**) as a mixture of two isomers (*E:Z*; 70:30). ^{1}H NMR δ 1.42 - 1.85 (m, 4H), 1.9 - 2.05 (m, 1.3H), 2.05 - 2.22 (m, 1H), 2.50 - 2.40 (m, 1H), 2.43 - 2.55 (m, 0.7H), 3.60 (td, J = 7.9, 4 Hz, 0.7H), 3.28 (dt, J = 10.6, 5.3 Hz, 0.3H), 3.45 - 3.74 (m, 2H), 3.53 (s, 2.1H), 3.63 (s, 0.9H), 3.84 - 4.07 (m, 1H), 4.55 (dt, J = 9.2, 6.6 Hz, 0.3H), 4.83 (dt, J = 11.9, 6.6 Hz, 0.7H), 6.04 (d, J=6.6 Hz, 0.3H), 6.40 (d, J = 11.9 Hz, 0.7H). IR (film) (cm^{-1}): 3400, 2920, 2850, 1650, 1450, 1205, 1100. Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.47; H, 9.75. Found: C, 64.60; H, 9.66.

(1S*,6R*)-4-Bromo-3-methoxy-2.7-dioxabicyclo[5.4.0]undecane 19. The reaction conditions were those used for the preparation of compound **13**. Starting from **18** (0.61 mmol, 113 mg), we obtained product **19** (50

mg, 31% yield) after flash chromatography on silica gel (ether:pentane; 10:90) as a mixture of three diastereoisomers. First eluted fraction, 2 isomers (80:20). ^{1}H NMR δ 1.40 - 2.40 (m, 8H), 3.10 - 3.30 (m, 0.4H), 3.36 (s, 2.4H), 3.43 (s, 0.6H), 3.46 - 3.68 (m, 1.6H), 3.68 - 3.90 (m, 2H), 3.90 - 4.10 (m, 0.2H), 4.20 (t, J = 3.3 Hz, 0.8H), 4.62 (d, J = 3 Hz, 0.2H), 4.72 (s, 0.8H). ^{13}C NMR δ major isomer 20.1, 28.8, 34.4, 34.5, 48.3, 54.8, 68.9, 73.0, 73.3, 99.3. minor isomer 20.0, 28.9, 29.7, 34.2, 36.4, 44.8, 55.3, 71.9, 77.3, 97.7. MS EI (*m/z*, %): 41 (35), 57 (21), 67 (23), 85 (100), 98 (45), 265 (0.08). IR (film) (cm^{-1}): 2950, 2880, 1450, 1140, 1030. Anal. Calcd. for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.62; H, 6.68. Second eluted fraction, 1 isomer. ^{1}H NMR δ 1.40 - 2.30 (m, 7H), 2.40 (dt, J = 12.7, 4.2 Hz, 1H), 3.15 - 3.50 (m, 2H), 3.54 (s, 3H), 3.62-3.93 (m, 3H), 4.32 (d, J = 8.5 Hz, 1H). ^{13}C NMR δ 19.8, 29.1, 34.0, 41.4, 46.3, 57.1, 69.1, 77.2, 79.8, 104.8. MS EI (*m/z*, %): 41 (34), 57 (23), 67 (23), 85 (74), 98 (100), 265 (0.30). IR (film) (cm^{-1}): 2950, 2880, 1460, 1125, 1060. Anal. Calcd. for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.51; H, 6.53.

REFERENCES

1. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
2. Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J.L.; Martin, J.D. *Chem. Rev.* **1995**, *95*, 1953. Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849.
3. For some recent results see: Oishi, T.; Nagumo, Y.; Hirama, M. *J. C. S., Chem. Comm.* **1998**, 1041. Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917. Gleason, M.M.; McDonald, F.E. *J. Org. Chem.* **1997**, *62*, 6432. Clark, J.S.; Kettle, J.G. *Tetrahedron Lett.* **1997**, *38*, 127. Atsuta, H.; Fujiwara, K.; Murai, A. *Synlett.* **1997**, 307. Alvarez, E.; Pérez, R.; Rico, M.; Rodriguez, M. R.; Martin, J. D. *J. Org. Chem.* **1996**, *61*, 3003.
4. Hemibrevetoxin B: Nicolaou, K.C.; Reddy, K.R.; Skokotos, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. Kadota, I.; Park, J.Y.; Koumura, N.; Polland, G.; Matsokawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777. Ishihara, J.; Murai, A. *Synlett* **1996**, 363. Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365. Mori, Y.; Yaegashi, K. Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557.
   Brevetoxin B: Nicolaou, K.C.; Theodorakis, E.E.; Rutjes, F.P.J.T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. Nicolaou, K.C.; Rutjes, F.P.J.T.; Theodorakis, E.A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173. See: Nicolaou, K.C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 589.
5. Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 683 and 1525. Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668. Paquet, F.; Sinaÿ, P. *Tetrahedron Lett.* **1984**, *25*, 3071. Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5413. Doyle, M. P.; Griffin, J.H., Chinn, M. S.; Van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917. Ha, D.-C.; Hart, D. J. *Tetrahedron Lett.* **1987**, *28*, 4489. Kerwin, S.M.; Paul, A.G.; Heathcock, C.H. *J. Org. Chem.* **1987**, *52*, 1686. Koft, E. R.; Dorff, P.; Kullnig, R. *J. Org. Chem.* **1989**, *54*, 2936. Fabre, V.; Lila, C.; Saroli, A.; Doutheau, A. *Tetrahedron* **1989**, *45*, 7765. Vlahov, I. R.; Vlahova, P. I.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 7503. Maudrin, J.; Barrère, B.; Chantegrel, B.; Deshayes, C.; Quash, G.; Doutheau, A. *Bull. Soc. Chim. Fr.* **1994**, *131*, 400. Devasagayaraj, A.; Schwink, L.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 3311.
6. Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793.
7. Sweet, F.; Brown, R.K. *Can. J. Chem.* **1966**, *44*, 1571.
8. Fleming, I.; Dunogués, J.; Smithers, R. *Organic Reactions*, **1989**, *37*, 57.
9. Hunter, R.; Michael, J.P.; Tomlinson, G.D. *Tetrahedron* , **1994**, *50*, 871.
10. Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Ogilvie, W.W.; Yiannikouros, G.; Prasad, C.V.C.; Veale, C.A.; Hark, R.R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.