128.8, 128.6 (Ph), 99.4, 99.1 (CH_2OMe), 83.5, 81.8, 75.5, 74.7, 74.6, 72.3 (CH, inositol), 56.4, 56.3 (OMe), 27.7 (*CMe*), 20.1 (*CMe*).

1D-1,6-*O*-(1,1,3,3-Tetraisopropyldisiloxanedi-1,3-yl)-*myo*-inositol (46). (a) The deprotection of crude **31a** obtained from **1a** (20.0 g, 63.7 mmol) with chloroform-TFA (330 mL, 10:1 v/v) at room temperature was complete within 4 h at room temperature with only little isomerization observed. Chromatography on silica gel (chloroform-methanol, 9:1) afforded **46** (22.6 g, 84%) as a glassy solid. (b) The diol **31a** (487 mg, 0.87 mmol) was deprotected analogously as described above for triol **7**. The product was purified by silica gel chromatography as above giving **46** (225 mg, 61%): TLC R_f 0.22 (chloroform-methanol, 9:1); $[\alpha]_D$ +8.5° (*c* 3.4, MeOH); ^1H NMR (DMSO-d_6) δ 4.58, 4.51, 4.45, 4.39 (each d, OH), 3.72 (m, H-2, H-6, 2 H), 3.51 (dd, H-1, J = 2.8, 9.1 Hz, 1 H), 3.41 (d tr, H-4, J = 4.6, 9.4 Hz, 1 H), 3.19 (ddd, H-3, J = 5.3, 2.5, 9.7 Hz, 1 H), 3.03 (d tr, H-5, J = 4.6, 8.9 Hz, 1 H), 1.07-0.9 (m, *i*-Pr, 28 H); ^{13}C NMR ($CDCl_3$) δ 76.2, 74.5, 74.1, 72.8, 71.8, 71.4 (broad signals, CH, inositol), 17.22, 17.17 (CH*Me*), 12.7, 12.05 (*C*HMe).

1D-1,6-*O*-(1,1,3,3-Tetraisopropyldisiloxanedi-1,3-yl)-2,3,4,5-*O*-tetrakis(methoxymethylene)-*myo*-inositol (47). Tetrol **46** (10.0 g, 23.7 mmol) was alkylated with MOM-Cl (9.5 mL) in DMF (50 mL) in the presence of *i*-Pr_2EtN (15.9 g, 20% excess). The mixture was stored at room temperature during 12 h and next heated at 60 °C during 5 h. The product was purified by silica gel chromatography (hexane-acetone, 10:1) giving **47** as a thick oil (12.04 g, 85%): TLC R_f 0.26 (hexane-acetone, 5:1); $[\alpha]_D$ +30.3° (*c* 3.5, $CHCl_3$); ^1H NMR (C_6D_6) δ 5.03 (m, CH_2OMe, 5 H), 4.70 (m, CH_2OMe, 3 H), 4.26 (tr, H-6(4), J = 9.0 Hz, 1 H), 4.24 (tr, H-4(6), J = 9.8 Hz, 1 H), 4.14 (tr, H-2, 2.5 Hz, 1 H), 3.47 (m, H-5, H-3, H-1, 3 H), 3.40, 3.39, 3.33, 3.29 (each s, Me, 3 H), 1.18-0.94 (m, *i*-Pr, 28 H); ^{13}C NMR (C_6D_6) δ 98.8, 98.7, 97.8, 96.0 (CH_2OMe), 80.4, 77.8, 76.9, 76.3, 76.0, 75.9 (CH, inositol), 56.4, 56.2, 55.4, 55.3 (OMe), 17.68-17.29 (seven signals, CH*Me*), 13.2, 13.0, 12.6, 12.4 (*C*HMe); MS (EI) 491 (MI - $2C_2H_5O$, -OH), 387 (5), 357 (5), 303 (2), 277 (6), 263 (9), 249 (11), 109 (3), 45 (BP).

1D-2,3,4,5-*O*-Tetrakis(methoxymethylene)-*myo*-inositol (48). Fully protected derivative **47** (11.6 g, 19.4 mmol) was treated with tetra-*n*-butylammonium fluoride in THF (43 mL, 1.0 M). After 0.5 h the mixture was concentrated and chromatographed on silica gel (hexane-acetone, 3:1, then 1:1) to give pure **48** (6.7 g, 97%): $[\alpha]_D$ +3.6° (*c* 1.2, $CHCl_3$); TLC R_f 0.23 (hexane-acetone, 1:1); ^1H NMR (C_6D_6) δ 4.92-4.56 (m, CH_2, 8 H), 4.19 (dd, H-4(5), J = 9.3, 10.0 Hz, 1 H), 4.14 (tr, H-2, J = 2.5 Hz, 1 H), 3.93 (tr, H-5(4), J = 9.5 Hz, 1 H), 3.47 (dd, H-3, J = 2.6, 10.1 Hz, 1 H), 3.31, 3.23, 3.22, 3.10 (each s, Me, 3 H), 3.3-3.2 (m, H-1, H-6, 2 H); ^{13}C NMR (C_6D_6) δ 98.5, 98.3, 97.9, 96.2 (CH_2OMe), 85.3, 77.4, 76.9, 76.5, 73.3, 72.3 (CH, inositol), 55.8, 55.5, 55.4 (OMe); MS (EI) m/z 311 (MI - C_2H_5O), 279 (MI - C_2H_5O, $-CH_4O$), 261 (MI - C_2H_5O, $-CH_4O$, $-H_2O$), 217, 187, 161, 130, 109, 73, 45 (BP).

1D-2,3,4,5-*O*-Tetrabenzoyl-*myo*-inositol (50). Tetrol **46** (202 mg, 0.48 mmol) was refluxed in pyridine with benzoyl chloride/DMAP during 24 h. After the aqueous workup the residue was dissolved in acetonitrile containing 10% aqueous HF (50%), and the solution was kept at 45 °C during 12 h. The mixture was neutralized with aqueous potassium bicarbonate and concentrated, and the residue was chromatographed to give **50** (237 mg, 83%, noncrystalline solid): TLC R_f 0.56 (chloroform-methanol, 9:1); $[\alpha]_D$ +75° (*c* 1.2, MeOH); ^1H NMR ($CDCl_3$) δ 8.05 (m, Ph, 4 H), 7.85 (m, Ph, 2 H), 7.55-7.2 (m, 12 H), 6.22 (tr, H-4, J = 10.2 Hz, 1 H), 6.12 (tr, H-2, J = 2.8 Hz, 1 H), 5.81 (tr, H-5, J = 9.8 Hz, 1 H), 5.68 (dd, H-3, J = 2.8, 10.5 Hz, 1 H), 4.40 (tr, H-6, J = 9.7 Hz, 1 H), 4.22 (dd, H-1, J = 2.8, 9.8 Hz, 1 H), 4.05 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 166.6, 166.2, 165.7, 165.5 (each C=O), 133.3, 133.2, 133.1, 133.0, 129.9, 129.7, 129.5, 129.3, 129.2, 128.5, 128.3, 128.2 (Ph), 73.6, 72.2, 71.4, 70.6, 70.5, 70.3 (CH, inositol). Anal. Calcd for $C_{34}H_{28}O_{10}$: C, 68.38; H, 4.73. Found: C, 68.42; H, 4.95.

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Intramolecular Palladium-Catalyzed 1,4-Addition to Conjugated Dienes. Stereoselective Synthesis of Fused Tetrahydrofurans and Tetrahydropyrans

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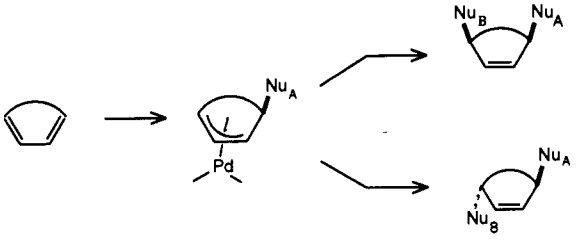
Abstract: Palladium-catalyzed oxidation of diene alcohols **2a**, **2b**, **4a**, **4b**, **5**, and **6** led to an intramolecular 1,4-addition to the conjugated diene to yield fused tetrahydrofurans or tetrahydropyrans. The reactions were run in acetone-acetic acid (4:1) or in an alcohol as the solvent, and the oxidant employed was *p*-benzoquinone. The catalyst used was palladium acetate. The reactions proceed via a heterocyclic (π-allyl)palladium complex, which is formed by intramolecular attack of the alcohol function on a (π-diene)palladium complex. Attack by acetate, chloride, or an alcohol on the π-allyl intermediate leads to an overall 1,4-oxyacetoxylation, 1,4-oxychlorination, or 1,4-oxyalkoxylation, respectively. In the intramolecular 1,4-oxyacetoxylation it was possible to obtain dual stereocontrol in most cases, i.e., the reaction can be directed toward either a cis or trans oxyacetoxylation across the diene. These new procedures allow the preparation of fused [6,5], [7,5], [6,6], and [7,6] tetrahydrofurans and tetrahydropyrans.

Nucleophilic additions to unsaturated hydrocarbons coordinated to a transition metal are important in organic synthesis.[1-3] In many cases these reactions are part of a catalytic process. The stereochemistry of the nucleophilic addition is of great interest, and the nucleophile may attack the hydrocarbon ligand from the same face as the metal or the opposite face. It is of particular

Scheme I



(1) (a) Bäckvall, J. E. In *Reaction of Coordinated Ligands*; Braterman, P. S., Ed.; Plenum Press: New York, 1986; Vol. 1, p 679. (b) Bäckvall, J. E. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: London, 1989; Vol. 1, p 135. (c) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415. (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (e) Tsuji, J. *Tetrahedron* **1986**, *42*, 4095.

(2) (a) Pearson, A. J. In *Reaction of Coordinated Ligands*; Braterman, P. S., Ed.; Plenum Press: New York, 1986; Vol. 1, p 1. (b) Pearson, A. J.; Lay, Y. S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem.* **1989**, *54*, 3882. (c) Pearson, A. J.; O'Brien, M. K. *J. Org. Chem.* **1989**, *54*, 4663. (d) Turnbull, M. M.; Foxman, B. M.; Rosenblum, M. *Organometallics* **1988**, *7*, 200. (e) Semmelhack, M. F.; Hanh, T. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 2715.

(3) (a) Faller, J. W.; Linebarrier, D. *Organometallics* **1988**, *7*, 1670. (b) Bäckvall, J. E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892.

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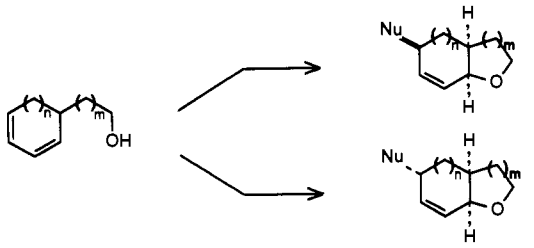
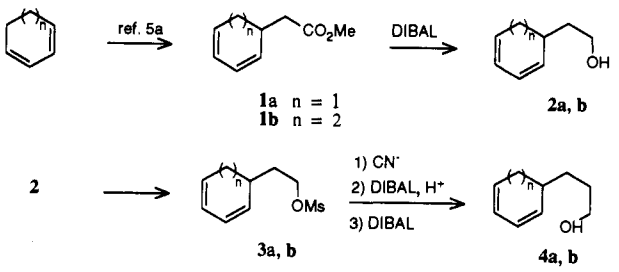
Scheme II



Scheme III



importance if one can alter the stereochemistry of the nucleophilic addition for a given nucleophile.

We have developed recently a number of palladium-catalyzed 1,4-additions to conjugated dienes that proceed via nucleophilic attack on (π-diene)- and (π-allyl)palladium complexes.[4-7] In a number of cases it is possible to obtain dual stereocontrol in the overall 1,4-addition. The stereochemical outcome is determined by the attack on the π-allyl intermediate by the second nucleophile (Scheme I). These stereoselective 1,4-additions were extended recently to lactonization reactions[5] and intramolecular amidation reactions.[6] In this paper we report on stereocontrolled palladium-catalyzed 1,4-additions to cyclic conjugated dienes, which involve an intramolecular oxypalladation of the diene in the first step (Scheme II). In this way a number of stereodefined fused tetrahydrofurans and tetrahydropyrans are readily available.

Results and Discussion

A. Preparation of Starting Materials. The synthesis of diene ester **1** from the corresponding diene has been described previously.[5,6,8] Reduction of this ester with diisobutylaluminum hydride (DIBAL) afforded the dienol **2**, which was the starting material for the preparation of fused tetrahydrofurans. Diene alcohol **2** was transformed to its higher homologue **4** via the mesylate **3** followed by reaction with CN^- and subsequent reduction (Scheme III).[9]

B. Palladium-Catalyzed Oxyacetoxylation and Oxychlorination. The dienols **2** and **4** were subjected to a palladium-catalyzed oxidation in acetone[4b] in the presence of acetic acid. Palladium acetate was used as the catalyst, and *p*-benzoquinone was employed as the oxidant. The reaction was performed under three different reaction conditions: A (no LiCl), B (0.2 equiv of LiCl), and C (2 equiv of LiCl). These slight variations of reaction conditions had a dramatic effect on the outcome of the reaction and gave in each case a different product with complete product control (Scheme IV).[10] Thus in the absence of LiCl (method A) the

Scheme IV

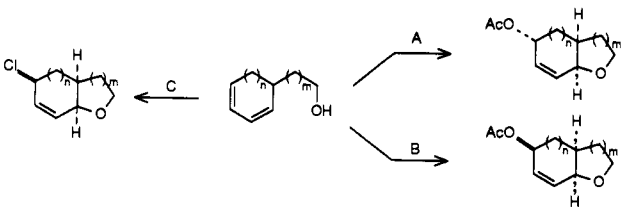


Table I. Palladium-Catalyzed Stereocontrolled Intramolecular Trans and Cis 1,4-Oxyacetoxylation of Conjugated Dienes[a]

entry	starting material	method	product	% yield[b]	stereochem.[c]
1	**2a**	A	**7**	87	>98% trans
2		B	**8**	82	cis : trans = 91 : 9
3	**4a**	A	**9**	87	>98% trans
4		B	**10**	78	cis : trans = 91 : 9
5	**5**	A	**11**	85	>98% trans
6		B	**12**	86	cis : trans = 90 : 10
7	**6**	A	**13**	65	>98% trans
8	**2b**	A	**14**	90	>98% trans
9		B	**15**	81	>98% cis
10	**4b**	A	**16**	86	cis : trans = 25 : 75
11		B	**17**	84	>98% cis

[a] The reactions were performed in acetone–acetic acid (4:1) using 5 mol % of $Pd(OAc)_2$ and 2 equiv of *p*-benzoquinone. Method A: in the absence of LiCl. Method B: 0.2 equiv of LiCl. [b] Isolated yield of pure product. [c] Refers to the addition across the diene system. In all cases the bridgehead protons were cis to one another (>99%).

reaction proceeded to give the trans-oxyacetoxylation product, whereas in the presence of 0.2 equiv of LiCl (method B) the cis-oxyacetoxylation product was formed. The use of 2 equiv of LiCl (method C) resulted in the incorporation of chloride as a nucleophile, and a cis-1,4-oxychlorination product was formed with high stereoselectivity. Thus, oxidation of **2a** employing method A afforded **7** in 87% yield with >98% *trans* addition, whereas method B gave **8** in 82% yield with 91% cis addition (Table I, entries 1 and 2). At an increased LiCl concentration (method C) **2a** afforded allylic chloride **18** in 91% yield in a highly stereoselective cis addition (>98% cis) (Table II, entry 1). The corresponding oxidations of the three-carbon chain analogue **4a**

(4) (a) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B.; *Acta Chem. Scand.* **1990**, *44*, 492. (c) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

(5) (a) Bäckvall, J. E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, *30*, 137. (b) Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G. Manuscript to be published.

(6) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem.* 4Soc. **1990**, *112*, 3683.

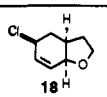
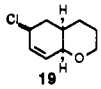
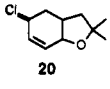
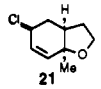
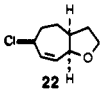
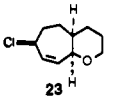
(7) Bäckvall, J. E.; Andersson, P. G. *J. Org. Chem.* **1991**, *56*, 2274.

(8) Bäckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988.

(9) Because of the Swedish restrictions on the use of diazomethane, the Arndt–Eistert homologation could not be used in the present case.

(10) The effect of chloride on the reaction pathway has been demonstrated previously in both intermolecular and intramolecular 1,4-oxidations.[4-7]

Table II. Palladium-Catalyzed Intramolecular Cis 1,4-Oxychlorination of Conjugated Dienes[a]

entry	starting material	reaction time (h)[b]	product	% yield[c]	stereochem.[d]
1	 **2a**	12 + 0	 **18**	91	>98% cis
2	 **4a**	12 + 12	 **19**	89	>98% cis
3	 **5**	12 + 24	 **20**	90	>98% cis
4	 **6**	12 + 24	 **21**	72	>98% cis
5	 **2b**	12 + 0	 **22**	88	>98% cis
6	 **4b**	12 +12	 **23**	81	>98% cis

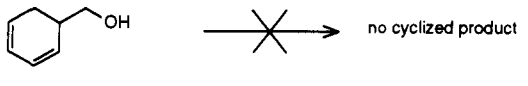
[a] The reactions were performed as in Table I but in the presence of 2 equiv of LiCl (method C). [b] In all cases the addition time of the diene was 12 h. The second figure refers to the reaction time after completed addition. [c] Isolated yield of pure product. [d] Refers to the addition across the diene system. In all cases the bridgehead protons were cis to one another (>99% cis).

led to useful hexahydrobenzopyran derivatives (entries 3 and 4, Table I, and entry 2, Table II). Also the cycloheptadiene derivatives **2b** and **4b** with a two- and a three-carbon chain, respectively, afforded the corresponding fused tetrahydrofurans and tetrahydropyrans.

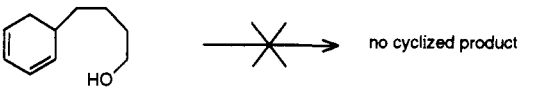
In most cases it was possible to completely alter the stereochemistry of the intramolecular 1,4-oxyacetoxylation from an overal trans addition to an overall cis addition (Table I). The stereoselectivity was sometimes high, and a trans oxyacetoxylation (>98% trans) was obtained with **2a**, **4a**, **5**, **6**, and **2b** (entries 1, 3, 5, 7, 8, Table I). The corresponding stereoselectivity for the cis oxyacetoxylation (method B) was >90% cis in all cases tried, and for dienes **2b** and **4b** it was even higher (>98% cis). Cyclization of **2b** to fused tetrahydrofurans **14** and **15** went with complete dual stereocontrol (entries 8 and 9, Table I). Thus oxidation of **2b** in the absence of LiCl (method A) afforded **14** in 90% yield with >98% trans addition. In the presence of chloride ligands (method B), **2b** gave **15** in 81% yield with >98% cis addition.

The use of 2 equiv of LiCl (method C) gave a highly stereoselective 1,4-oxychlorination in all cases tried (Table II). These fused tetrahydrofurans and tetrahydropyrans with an allylic chloride are useful for further synthetic transformations (vide infra).

The intramolecular oxyacetoxylation and oxychlorination work well for six- and seven-membered dienes with two- and three-carbon chains. Thus, fused [6,5], [6,6], [7,5], and [7,6] tetrahydrofurans and tetrahydropyrans are efficiently prepared by the present method. Attempts to prepare an annulated oxetane system from **24** or a seven-membered cycle containing oxygen from **25** failed. Thus, the rate decrease in the formation of a four- or seven-membered ring is sufficient to inhibit the desired cyclization reaction, and instead an intermolecular 1,4-oxidation takes place.



24

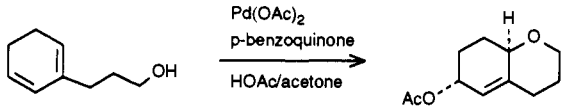


25

It was established that diene alcohols **24** and **25** under the conditions of method C underwent intermolecular 1,4-chloroacetoxylations to form a complex mixture of isomers in each case (cf. ref 4c).

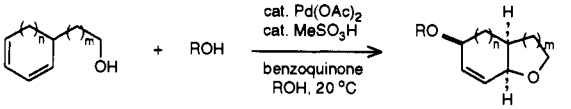
In a few cases the intramolecular oxyacetoxylation and oxychlorination were tested with respect to substituents in the side chain and on the diene. Substituents on the side chain do not seem to have any effect on the rate of the reaction. Thus, α,α-dimethyl alcohol **5** (entries 5 and 6, Table I, and entry 3, Table II) gave 85, 86, and 90% yields of the corresponding cis- and trans-oxyacetoxylation products **10** and **11** and cis–oxychlorination product **20**, respectively. Substitution at the 4-position of the diene decreases the rate of the reaction, and intramolecular oxyacetoxylation and oxychlorination of **6** afforded **13** and **21** in 65 and 72% yields, respectively (entry 7, Table I, and entry 4, Table II). The stereoselectivity of the reactions, however, is still very high in both cases (>98%).

In all of the cases given in Tables I and II the side chain with the alcohol is situated in the 5-position of the diene. We have reported previously on the analogous reaction with the ω-hydroxylalkyl side chain in the 1-position, which leads to a synthetically useful spirocyclization.[7] We have now also studied one case where the alcohol chain is situated in the 2-position of the diene. Thus palladium-catalyzed oxidation of **26** using the reaction conditions of method A afforded allylic acetate **27** in 60% yield in a highly stereoselective trans 1,4-addition. This kind of stereodefined product with an unsaturation at one of the carbons at the bridgehead is of synthetic interest, because a trans-fused heterocycle, which is alkyl substituted in the bridge, may be obtained via an organocopper S_N2' substitution of the acetate.[11]



26 **27** (> 98 % trans)

C. Palladium-Catalyzed Oxyalkoxylation. The palladium-catalyzed addition of two alkoxy groups to a conjugated diene in intermolecular reactions has been reported previously from our laboratory.[12] The key to the success of this reaction was to add a catalytic amount of a strong acid such as methanesulfonic acid, which increases the reactivity of the intermediate (π-allyl)palladium complex. These reaction conditions were employed in the palladium-catalyzed reaction of diene alcohols **2** and **4**, which afforded fused tetrahydrofurans and tetrahydropyrans via an intramolecular 1,4-oxyalkoxylation (eq 1, Table III). The reaction

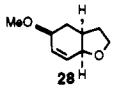
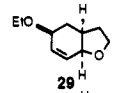
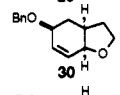
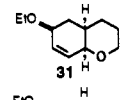
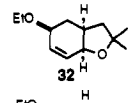
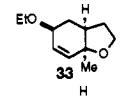
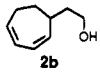
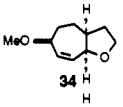
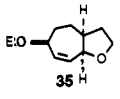
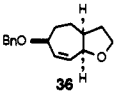
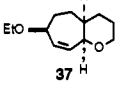


(1)

was performed using the appropriate alcohol as the solvent and by slow addition of the diene. In all cases tried, the reaction was stereoselective and gave the cis-1,4-addition product in 87–98% stereoselectivity. This is consistent with an external attack by the alcohol on the intermediate (π-allyl)palladium complex[12] (vide infra). The cycloheptadiene alcohols **2b** and **4b** and cyclohexadiene alcohol **4a** gave the cyclization product in a very high stereoselectivity (>98% cis addition), whereas the corresponding cyclohexadiene alcohol **2a** afforded a cyclization product with an overall cis:trans addition ratio of 90:10 (Table III). The methyl-substituted alcohol **6** gave an even lower stereoselectivity, and the oxymethoxylation product was produced in a cis:trans addition

(11) (a) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (c) Bäckvall, J. E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615.
(12) Bäckvall, J. E.; Vågberg, J. O. *J. Org. Chem.* **1988**, *53*, 5695.

Table III. Palladium-Catalyzed Intramolecular Trans 1,4-Oxyalkoxylation of Conjugated Dienes[a]

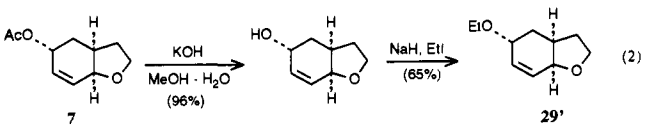
entry	starting material	solvent	product	% yield[b]	stereochem.[c]
1	 **2a**	MeOH	 **28**	75	cis : trans = 91 : 9
2		EtOH	 **29**	85	cis : trans = 90 : 10
3		BnOH	 **30**	75	cis : trans = 90 : 10
4	 **4a**	EtOH	 **31**	86	>98% cis
5	 **5**	EtOH	 **32**	83	cis : trans = 91 : 9
6	 **6**	EtOH	 **33**	55	cis : trans = 87 : 13
7	 **2b**	MeOH	 **34**	74	>98% cis
8		EtOH	 **35**	87	>98% cis
9		BnOH	 **36**	85	>98% cis
10	 **4b**	EtOH	 **37**	85	>98% cis

[a] The reactions were performed in the appropriate alcohol using 5 mol % of $Pd(OAc)_2$, 2 equiv of *p*-benzoquinone, and 0.1 equiv of $MeSO_3H$. [b] Isolated yield of pure product. [c] Refers to the addition across the diene system. In all cases the bridgehead protons were cis to one another.

ratio of 87:13 (entry 6, Table III). The reason for the formation of the small amounts of trans-addition product is not clear, but it is interesting to note that the relative amount of anomalous trans-1,4-addition product increased if the diene alcohol was added not slowly but in one portion.

Three different alcohols MeOH, EtOH, and BnOH (Bn = benzyl) were tested in this reaction. They all proceeded smoothly, and diene alcohols **2a** and **2b** afforded yields of fused tetrahydrofurans in the range 73–85% for these alcohols (entries 1–3, 7–9, Table III). The use of benzyl alcohol is of particular synthetic interest since the benzyl group serves as a protective group that tolerates harsh reaction conditions.

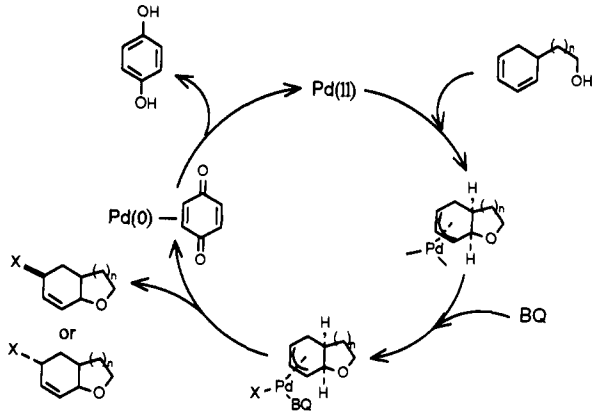
The stereochemistry of the adducts **29** and **35** was established by NOE experiments. Furthermore, the structure of the minor stereoisomer **29′** formed in the oxidation of **2a** (entry 2, Table III) was unambiguously established by an independent synthesis according to eq 2.



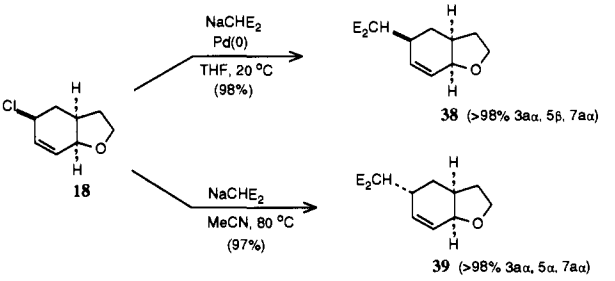
(2)

D. Mechanism of the Intramolecular 1,4-Oxidations. The catalytic cycle of these intramolecular 1,4-oxidations involves (π-allyl)palladium complexes, where a tetrahydrofuran or a tetrahydropyran has been formed by intramolecular attack by the alcohol on an initially formed (η^4-diene)palladium complex (Scheme V). Attack by alcohols on dienes coordinated to palladium(II) to give [(1,2,3-η)-4-alkoxyalkenyl]palladium complexes is well precedented in the literature.[3b,13,14] The oxypalladation reaction is known to occur with trans stereochemistry.[3b,15-17] Coordination of *p*-benzoquinone[18] to the heterocyclic (π-allyl)-palladium complex induces the nucleophilic attack. Depending on the reaction conditions, this attack can occur either cis or trans. During the latter process a Pd(0)–benzoquinone complex[19] may be formed, which on reaction with acid would disproportionate to hydroquinone and palladium(II).[20]

Scheme V

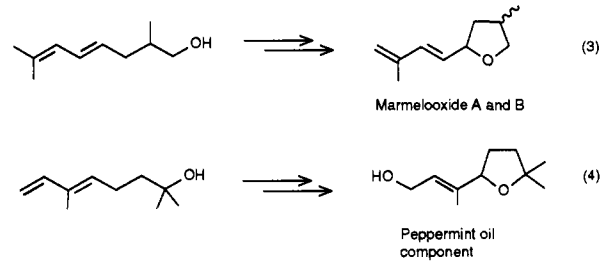


Scheme VI[a]



[a] E = CO_2Me.

E. Synthetic Applications. The present procedure allows for the preparation of a number of stereodefined tetrahydrofurans and tetrahydropyrans that are fused to a six- or seven-membered ring. The reaction also works well with acyclic dienes, and this was recently applied to the synthesis of naturally occurring tetrahydrofurans (eqs 3 and 4).[21] Thus, Marmelo oxides A and B



(3)
(4)

(13) (a) Rowe, J. M.; White, D. A.; *J. Chem. Soc.* **1967**, 1451. (b) Robinson, S. D.; Shaw, B. L. *J. Chem. Soc.* **1964**, 5002.
(14) Lukas, J.; Leeuven, P. W. N. M.; Volger, H. C.; Kouwenhoven, A. P. J. *J. Organomet. Chem.* **1973**, *47*, 153.
(15) Stille, J. K.; Morgan, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 5135.
(16) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806.
(17) Bäckvall, J. E.; Nordberg, R. E.; Zetterberg, K.; Åkermark, B. *Organometallics* **1983**, *2*, 1625.
(18) Bäckvall, J. E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243.
(19) Hiramatsu, M.; Shiozaki, K.; Fujinami, T.; Sakai, S. *J. Organomet. Chem.* **1983**, *246*, 203.
(20) It has been reported that protonation of a (*p*-benzoquinone)nickel(0) complex produces hydroquinone and Ni(II): Uhlig, E.; Fischer, R.; Krimse, R. *J. Organomet. Chem.* **1982**, *239*, 385.

and a terpene alcohol from peppermint oil were prepared from acyclic precursors.

The heterocyclic products shown in Table I contain an allylic acetate in the 5- or 6-position, which can function as a leaving group in a number of transition-metal-catalyzed (Pd, Cu, Mo, Fe, Ni) reactions. The latter transformations are usually highly stereospecific, and the fact that the allylic acetate can be obtained either cis or trans to the bridgehead makes a number of stereodefined heterocycles available. The fused tetrahydrofurans and tetrahydropyrans in Table II have a chloride as a leaving group in the corresponding position. The synthetic utility of these compounds is enhanced by the fact that the chloride can be replaced with either retention or inversion.[4c] To demonstrate this point, compound **18** was transformed into **38** and **39** with full stereocontrol (Scheme VI). Thus, palladium-catalyzed reaction of **18** with sodium dimethyl malonate at room temperature proceeded with complete retention of configuration at the 5-position of the hexahydrobenzofuran. The corresponding reaction between **18** and the dimethyl malonate anion in the absence of catalyst at an elevated temperature occurred with inversion.

Conclusion

An efficient and new approach for the stereocontrolled preparation of fused tetrahydrofurans and tetrahydropyrans has been developed. The reactions utilize readily available 5-(ω-hydroxyalkyl)-1,3-cycloalkadienes and offer a choice of stereochemistry in the intramolecular 1,4-addition. This dual stereocontrol is obtained by a slight variation in the ligand environment of the metal, and the underlying mechanism of the reaction is well understood.

Experimental Section

Unless stated otherwise, NMR spectra were recorded for $CDCl_3$ solutions with a Varian XL 300 spectrometer, ^1H NMR at 300 MHz and ^{13}C NMR at 75.4 MHz, using tetramethylsilane (0.0 ppm, ^1H NMR) or chloroform-d_1 (77.0 ppm, ^{13}C NMR) as internal standard. Spectral assignments were made with the aid of COSY-45 experiments. Selected NOEs were quantified by NOE difference spectra. Samples for NOE measurements were prepared in the appropriate solvent and degassed by flushing with argon for 15 min. NOE difference spectra were obtained with 10–15-s preirradiation. NOE effects were corrected for incomplete saturation of the target proton. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using a 0.1-mm KBr cell with CCl_4 as solvent. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument either in the electron impact mode using a potential of 110 eV or in the chemical ionization mode with methane as reagent gas. Microanalyses were performed by Analytische Laboratorien, Engelskirchen, FRG. Slow addition of dienes was performed by the use of a Sage Instruments Model 355 syringe pump. Commercial acetone (99.5%), acetic acid (99.8%), carbon tetrachloride (99.9%), ethanol (99.5%), methanol (99.5%), and benzyl alcohol (>97%) were used as delivered. 1,4-Benzoquinone, lithium chloride, and lithium acetate dihydrate were purchased from Aldrich and used without further purification. Palladium acetate (47.09% Pd) was purchased from Engelhard, Gloucestershire, England. Merck silica gel 60 (240–400 mesh) was used for column chromatography.

Synthesis of Diene Alcohols 2a and 2b. **1a**, **1b**, **2a**, and **2b** were synthesized according to refs 5a and 8. For an alternative synthesis of **1b**, see ref 22.

2b: ^1H NMR δ 5.88–5.72 (m, 4 H), 3.75 (app q, 2 H), 2.59 (m, 1 H), 2.35 (app q, 2 H), 1.89–1.57 (m, 4 H), 1.40 (br s, 1 H); ^{13}C NMR δ 137.5, 134.2, 124.7, 124.3, 60.8, 38.5, 37.5, 30.8, 29.1.

Synthesis of Diene Alcohols 4a and 4b. Mesylates **3a** and **3b** were synthesized from alcohols **2a** and **2b** according to ref 6. The mesylates **3a** and **3b** were then converted into the corresponding nitriles (NaCN, THF–DMSO (1:1), 96–95%). The nitriles were reduced with DIBAL in a two-step procedure[23] to give **4a** and **4b** in 78 and 70% isolated yields based on **3a** and **3b**, respectively.

4a: ^1H NMR δ 5.87 (m, 2 H), 5.77 (m, 1 H), 5.69 (m, 1 H), 3.64 (t, 2 H), 2.35–2.22 (m, 2 H), 1.98 (m, 1 H), 1.67–1.36 (m, 5 H); ^{13}C NMR δ 131.2, 125.9, 124.0, 123.8, 63.1, 32.6, 30.5, 30.1, 28.6.

4b: ^1H NMR δ 5.82–5.70 (m, 4 H), 3.65 (dd, 2 H), 2.41 (m, 1 H), 2.34 (m, 2 H), 1.87–1.60 (m, 4 H), 1.56–1.33 (m, 3 H); ^{13}C NMR δ 137.9, 134.1, 124.7, 124.0, 63.1, 40.8, 31.8, 30.7, 30.2, 29.1.

Alcohol **5** was obtained in 95% yield from reaction of ester **1a** with 2.2 equiv of MeLi.

5: ^1H NMR δ 5.93–5.75 (m, 4 H), 2.48 (m, 1 H), 2.35 (m, 1 H) 2.03 (m, 1 H), 1.74 (dd, 1 H), 1.51 (dd, 1 H), 1.37 (br s, 1 H), 1.25 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR δ 132.5, 126.1, 124.1, 123.5, 71.3, 48.0, 30.3, 30.02, 29.96, 29.2.

Alcohol **6** was prepared from 1-acetoxy-4-chloro-3-methyl-2-cyclohexene[4c] according to the procedure described in refs 5a and 8 (cf. Scheme III).

6: ^1H NMR δ 5.84 (m, 1 H), 5.67 (m, 1 H), 5.55 (m, 1 H), 3.68 (m, 2 H), 2.37 (m, 1 H), 2.21–2.06 (m, 2 H), 1.80 (s, 3 H), 1.73–1.58 (m, 2 H), 1.32 (br s, 1 H); ^{13}C NMR δ 125.2, 124.5, 121.5, 119.4, 60.8, 33.6, 33.2, 27.4, 22.0.

General Procedures for Palladium(II)-Catalyzed Cyclization of Cyclic Conjugated Dienols. All reactions were performed at 25 °C in the appropriate solvent using 5 mol % of $Pd(OAc)_2$. Slow addition of the diene was performed with a Sage Model 355 syringe pump. The amount of the dienes in the reaction mixture was 0.4–0.5 mmol substrate/mL of solvent. Depending on the external nucleophile and the desired stereochemistry of the product, one of the following methods was used.

Method A. The diene (0.50 g) was added during 12 h to a well-stirred solution of 2 equiv of 1,4-benzoquinone and 5 mol % of $Pd(OAc)_2$ in aetone–acetic acid (4:1, 7.5 mL). After the reaction was complete according to TLC, ether (30 mL) was added, and the resulting solution was washed with NaOH (0.5 M, 2 × 10 mL), water (10 mL), and brine (5 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure, and the residue was chromatographed on silica gel (pentane–ether, 75:25) to give pure product.

Method B. The diene (0.50 g) was added during 12 h to a well-stirred solution of 0.2 equiv of LiCl, 2 equiv of 1,4-benzoquinone, and 5 mol % of $Pd(OAc)_2$ in acetone–acetic acid (4:1, 7.5 mL). After the reaction was complete according to TLC, the reaction mixture was worked up as in method A above.

Method C. The diene (0.50 g) was added during 12 h to a well-stirred solution of 2 equiv of LiCl, 2 equiv of 1,4-benzoquinone, and 5 mol % of $Pd(OAc)_2$ in acetone–acetic acid (4:1, 7.5 mL). After the reaction was complete according to TLC, the reaction mixture was worked up as in method A above.

Method D. The diene (0.50 g) was added during 12 h to a well-stirred solution of 2 equiv of 1,4-benzoquinone, 5 mol % of $Pd(OAc)_2$, and 10 mol % of methanesulfonic acid in the appropriate alcohol (5.0 mL). After the reaction was complete according to TLC, the reaction mixture was worked up as in method A above.

5-Acetoxy-2,3,3a,4,5,7a-hexahydro-(3aα,5α,7aα)-benzofuran (7). Method A was used on **2a** and gave **7** (87%, >98% trans): ^1H NMR δ 6.02 (dd, J = 3.4, 10.3 Hz, 1 H), 5.96 (dd, J = 3.7, 10.3 Hz, 1 H), 5.26 (app q, J = 4.3 Hz, 1 H), 4.21 (app q, J = 3.1 Hz, 1 H), 3.93 (app dt, J = 5.8, 8.2 Hz, 1 H), 3.78 (app dt, J = 6.4, 8.2 Hz, 1 H), 2.54 (m, 1 H), 2.14 (m, 1 H), 2.05 (s, 3 H), 1.82 (m, 2 H), 1.69 (m, 1 H); ^{13}C NMR δ 170.5, 130.8, 128.2, 73.6, 66.8, 66.1, 33.0, 30.8, 29.8, 21.1; IR (CCl_4) 2946, 2872, 1738, 1370, 1240, 1049, 998; MS m/z 182 (M^+, 0.3), 140 (22), 122 (64), 95 (51), 79 (32), 55 (56), 43 (100).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.64; H, 7.60.

5-Acetoxy-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (8). Method B was used on **2a** and gave **8** (82%, 91% cis): ^1H NMR δ 5.96 (ddd, J = 1.8, 3.5, 10.0 Hz, 1 H), 5.85 (ddd, J = 1.2, 1.7, 10.0 Hz, 1 H), 5.25 (m, 1 H), 4.07 (m, 1 H), 4.03 (dt, J = 7.2, 15.6 Hz, 1 H), 3.81 (dt, J = 5.6, 8.5 Hz, 1 H), 2.41 (m, 1 H), 2.19 (m, 1 H), 2.07 (s, 3 H), 1.97 (ddt, J = 1.0, 4.9, 12.2 Hz, 1 H), 1.72 (m, 1 H), 1.46 (dt, J = 10.0, 12.2 Hz, 1 H); ^{13}C NMR δ 170.7, 131.7, 127.8, 73.5, 69.4, 67.1, 34.6, 32.3, 30.4, 21.2; IR (CCl_4) 2956, 2870, 1739, 1369, 1240, 1048, 1027; MS m/z 182 (M^+, 0.3), 140 (11), 123 (43), 122 (47), 95 (46), 55 (54), 43 (100).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.70; H, 7.64.

6-Acetoxy-3,4,4a,5,6,8a-hexahydro-(3aα,6α,8aα)-2*H*-benzo[*b*]pyran (9). Method A was used on **4a** and gave **9** (87%, >98% trans); ^1H NMR δ 6.00 (dd, J = 4.3, 10.0 Hz, 1 H), 5.93 (dd, J = 4.2, 10.0 Hz, 1 H), 5.30 (app q, J = 4.0 Hz, 1 H), 3.92 (app t, J = 3.8 Hz, 1 H), 3.84 (m, J_{AB} = 10.9 Hz, 1 H), 3.47 (ddd, J = 2.5, 10.1, 10.9 Hz, 1 H), 2.20 (ddd, J = 4.6, 11.7, 13.9 Hz, 1 H), 2.06–1.96 (m, 1 H), 2.02 (s, 3 H), 1.88–1.59 (m, 4 H), 1.54 (app dt, J = 3.1, 13.9 Hz, 1 H), 1.39 (m, 1 H); ^{13}C NMR δ 170.5, 132.3, 128.4, 70.9, 67.3, 67.2, 28.9, 28.8, 27.1, 21.9, 21.2; IR (CCl_4) 2938, 2841, 1736, 1370, 1242, 1208, 1063; MS m/z 196 (M^+, 0.1), 154 (22), 137 (24), 136 (100), 95 (16), 43 (22).

(21) Andersson, P. G.; Bäckvall, J. E. *J. Org. Chem.* **1991**, *56*, 5349.
(22) Pearson, A. J.; Kole, S. L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060.
(23) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5250.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.12.

6-Acetoxy-3,4,4a,5,6,8a-hexahydro-(3aα,6β,8aα)-2*H*-benzo[*b*]pyran (10). Method B was used on **4a** and gave **10** (78%, 91% cis): ^{1}H NMR δ 5.90 (ddd, J = 1.8, 4.6, 10.0 Hz, 1 H), 5.81 (m, J_{AB} = 10.0 Hz, 1 H), 5.33 (m, 1 H), 3.95 (m, 1 H), 3.81 (br s, 1 H), 3.46 (m, 1 H), 2.07–1.94 (m, 1 H), 2.06 (s, 3 H), 1.86–1.64 (m, 5 H), 1.37 (m, 1 H); ^{13}C NMR δ 170.8, 131.5, 129.6, 70.9, 70.6, 68.4, 31.2, 28.5, 28.2, 21.7, 21.2; IR (CCl_4) 2938, 2841, 1939, 1370, 1241, 1067; MS m/z 196 (M^+, 0.3), 154 (23), 136 (100), 108 (21), 95 (45), 79 (23), 67 (25), 55 (26).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.13; H, 8.15.

5-Acetoxy-2,2-dimethyl-2,3,3a,4,5,7a-hexahydro-(3aα,5α,7aα)-benzofuran (11). Method A was used on **5** and gave **11** (85%, >98% trans): ^{1}H NMR δ 5.98 (ddd, J = 1.2, 3.4, 10.1 Hz, 1 H), 5.88 (ddd, J = 1.1, 3.8, 10.1 Hz, 1 H), 5.28 (app q, J = 4.7 Hz, 1 H), 4.35 (m, 1 H), 2.65 (m, 1 H), 2.07–1.90 (m, 2 H), 2.05 (s, 3 H), 1.80 (m, 1 H), 1.58 (dd, J = 7.2, 12.6 Hz, 1 H), 1.31 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR δ 170.6, 131.6, 127.5, 80.4, 72.9, 66.5, 43.1, 34.6, 30.14, 30.08, 28.5, 21.2; IR (CCl_4) 2972, 2870, 1739, 1368, 1240, 1024; MS m/z 210 (M^+, 0.1), 150 (37), 135 (37), 133 (26), 119 (49), 117 (59), 95 (46), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.28; H, 8.50.

5-Acetoxy-2,2-dimethyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (12). Method B was used on **5** and gave **12** (86%, 90% cis): ^{1}H NMR δ 5.95 (ddd, J = 1.9, 3.6, 10.1 Hz, 1 H), 5.84 (m, J_{AB} = 10.1 Hz, 1 H), 5.24 (dddd, J = 1.8 Hz, 1 H), 4.23 (m, 1 H), 2.42 (m, 1 H), 2.08 (dd, 8.4, 11.9, 1 H), 2.07 (s, 3 H), 1.96 (m, J_{AB} = 11.9 Hz, 1 H), 1.65–1.53 (m, 2 H), 1.35 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR δ 170.7, 131.4, 128.3, 80.9, 72.1, 69.6, 44.9, 35.9, 31.1, 30.3, 28.4, 21.3; IR (CCl_4) 2972, 1739, 1366, 1241, 1035; MS m/z 210 (M^+, 0.2), 151 (30), 150 (42), 135 (39), 117 (35), 95 (47), 91 (24), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.38; H, 8.55.

5-Acetoxy-7a-methyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (13). Method A was used on **6** and gave **13** (65%, >98% trans): ^{1}H NMR δ 5.69 (m, 2 H), 5.38 (app t, J = 6.3 Hz), 3.88–3.72 (m, 2 H), 2.29–2.03 (m, 3 H), 2.06 (s, 3 H), 1.87–1.72 (m, 2 H), 1.34 (s, 3 H); ^{13}C NMR δ 170.7, 135.6, 126.3, 78.6, 66.7, 65.3, 41.0, 30.0, 29.5, 25.7, 21.2; IR (CCl_4) 2971, 2870, 1740, 1371, 1240; MS m/z 196 (M^+, 0.2), 181 (9), 154 (45), 136 (24), 121 (100), 109 (36), 91 (35), 55 (32), 43 (96).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.24; H, 8.11.

6-Acetoxy-3,3a,4,5,6,8a-hexahydro-(3aα,5α,8aα)-2*H*-cyclohepta[*b*]-furan (14). Method A was used and gave **14** (90%, >98% trans): ^{1}H NMR δ 5.78 (dd, J = 2.4, 12.2 Hz, 1 H), 5.63 (dddd, J = 1.1, 2.2, 4.7, 12.2 Hz, 1 H), 5.28 (m, 1 H), 4.66 (m, 1 H), 3.95 (app dt, J = 3.6, 8.4 Hz, 1 H), 3.65 (app dt, J = 6.9, 8.4, 1 H), 2.56 (m, 1 H), 2.17–2.00 (m, 2 H), 2.04 (s, 3 H), 1.83 (m, 1 H), 1.72–1.33 (m, 3 H); ^{13}C NMR δ 170.2, 133.7, 126.0, 78.6, 72.1, 66.9, 41.3, 34.1, 29.4, 25.6, 21.2; IR (CCl_4) 2939, 2865, 1737, 1370, 1239, 1055, 1018; MS m/z 196 (M^+, 0.2), 154 (8), 136 (62), 121 (19), 109 (39), 55 (53), 43 (100).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.04; H, 8.11.

6-Acetoxy-3,3a,4,5,6,8a-hexahydro-(3aα,5β,8aα)-2*H*-cyclohepta[*b*]-furan (15). Method B was used and gave **15** (81%, >98% cis): ^{1}H NMR δ 5.63 (m, 1 H), 5.43 (m, 1 H), 4.64 (m, 1 H), 3.91 (app dt, J = 3.2, 8.5, 1 H), 3.58 (app dt, J = 6.6, 8.5 Hz, 1 H), 2.34 (m, 1 H), 2.14–2.01 (m, 1 H), 2.06 (s, 3 H), 2.00–1.88 (m, 1 H), 1.70–1.56 (m, 3 H), 1.55–1.43 (m, 1 H); ^{13}C NMR δ 170.4, 130.3, 126.7, 79.3, 71.6, 66.6, 39.6, 34.4, 28.9, 25.7, 21.2; IR (CCl_4) 2938, 2865, 1740, 1370, 1244, 1063; MS m/z 196 (M^+, 0.1), 153 (9), 136 (100), 121 (19), 109 (28), 43 (39).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.15; H, 8.18.

7-Acetoxy-2,3,4,4a,5,6,7,9a-octahydro-(4aα,7α,9aα)-cyclohepta[*b*]-pyran (16). Method A was used on **4b** and gave **16** (86%, 75% trans): ^{1}H NMR δ 5.81 (ddd, J = 1.3, 5.1, 12.4 Hz, 1 H), 5.74 (ddd, J = 1.0, 2.8, 12.4 Hz, 1 H), 5.37 (m, 1 H), 4.22 (m, 1 H), 3.86 (ddd, J = 3.4, 5.2, 11.2 Hz, 1 H), 3.57 (ddd, J = 3.9, 8.3, 11.2 Hz, 1 H), 2.05 (s, 3 H), 2.00–1.59 (m, 8 H), 1.43 (m, 1 H); ^{13}C NMR δ 170.2, 133.2, 131.0, 76.4, 73.2, 66.8, 37.6, 30.8, 29.8, 25.6, 23.3, 21.3; IR (CCl_4) 2936, 2855, 1738, 1370, 1242, 1078; MS m/z 210 (M^+, 0.4), 168 (19), 150 (93), 135 (21), 123 (24), 121 (21), 109 (24), 97 (26), 91 (21), 79 (28), 55 (33), 43 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.36; H, 8.55.

7-Acetoxy-2,3,4,4a,5,6,7,9a-octahydro-(4aα,7β,9aα)-cyclohepta[*b*]-pyran (17). Method B was used on **4b** and gave **17** (84%, >98% cis): ^{1}H NMR δ 5.67–5.57 (m, 2 H), 5.38 (m, 1 H), 4,43 (m, 1 H), 3.78–3.60 (m, 2 H), 2.10–2.01 (m, 1 H), 2.06 (s, 3 H), 1.95–1.55 (m, 7 H), 1.49 (m, 1 H); ^{13}C NMR δ 170.3, 131.5, 131.1, 77.3, 73.6, 63.8, 36.8, 28.2, 27.0, 26.1, 25.3, 21.3; IR (CCl_4), 2936, 2854, 1737, 1370, 1243, 1076; MS m/z 210 (M^+, 0.2), 150 (100), 135 (18), 123 (25), 97 (20), 79 (21), 55 (28), 43 (85).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.57.

5-Chloro-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (18). Method A was used and gave **18** (91%, >98% cis): ^{1}H NMR δ 5.99 (d, J = 10.2 Hz, 1 H), 5.93 (ddd, J = 1.7, 3.2, 10.2 Hz, 1 H), 4.46 (app ddq, J = 1.7, 3.4, 5.1 Hz, 1 H), 4.02 (app dt, J = 6.9, 8.2 Hz, 2 H), 3.80 (app dt, J = 5.6, 8.5 Hz, 1 H), 2.35 (m, 1 H), 2.27–2.10 (m, 2 H), 1.83–1.68 (m, 2 H); ^{13}C NMR δ 133.6, 127.2, 72.9, 67.0, 54.4, 36.1, 35.4, 32.1; IR (CCl_4) 2957, 2868, 1077, 1062, 994; MS m/z 157 (M^+ – 1, 1.3), 123 (100), 95 (37), 79 (28), 77 (28), 67 (28), 55 (40), 39 (30).

Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99. Found: C, 60.41; H, 6.92.

6-Chloro-3,4,4a,5,6,8a-hexahydro-(4aα,6β,8aα)-2*H*-benzo[*b*]pyran (19). Method C was used and gave **19** (89%, >98% cis): ^{1}H NMR δ 5.95 (m, J_{AB} = 10.0 Hz, 1 H), 5.86 (m, J = 1.7, 4.7, 10.0 Hz, 1 H), 4.55 (app qq, J = 1.3, 6.0, 10.3 Hz, 1 H), 3.97 (m, J_{AB} = 11.2 Hz, 1 H), 3.46 (app dt, J = 2.0, 11.2 Hz, 1 H), 2.31 (app dt, J = 10.3, 12.7 Hz, 1 H), 1.93 (m, J_{AB} = 12.7 Hz, 1 H), 1.88–1.65 (m, 5 H), 1.38 (m, 1 H); ^{13}C NMR δ 133.6, 128.8, 70.4, 68.4, 55.9, 33.5, 33.0, 28.5, 21.6; IR (CCl_4) 2938, 2842, 1216, 1100, 1066; MS m/z 171 (M^+ – 1, 0.1), 138 (10), 137 (100), 91 (11), 79 (11), 77 (14), 39 (11), 29 (18).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.32; H, 7.44.

5-Chloro-2,2-dimethyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (20). Method C was used on **5** and gave **20** (90%, >98% cis): ^{1}H NMR δ 5.98 (m, J_{AB} = 10.3 Hz, 1 H), 5.92 (ddd, J = 1.5, 3.2, 10.3 Hz, 1 H), 4.45 (app qq, J = 1.7, 5.2 Hz, 1 H), 4.19 (m, 1 H), 2.35 (m, 1 H), 2.13 (app dt, J = 12.2, 4.8 Hz, 1 H), 2.07 (dd, J = 8.5, 12.9 Hz, 1 H), 1.86 (app dt, J = 12.2, 9.7 Hz, 1 H), 1.66 (dd, J = 3.7, 12.9 Hz, 1 H), 1.36 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR δ 133.3, 127.8, 80.8, 71.4, 54.5, 44.7, 37.3, 36.0, 30.3, 28.4; IR (CCl_4) 2973, 2875, 2842, 1148, 1058; MS m/z 186 (M^+, 0.4), 168 (62), 151 (100), 114 (34), 74 (30), 72 (43), 71 (43), 58 (52).

Anal. Calcd for $C_{10}H_{15}OCl$: C, 64.34; H, 8.10. Found: C, 64.20; H, 7.97.

5-Chloro-7a-methyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (21). Method C was used on **6** and gave **21** (72%, >98% cis): ^{1}H NMR δ 5.84 (dd, J = 2.7, 10.2 Hz, 1 H), 5.72 (dd, J = 1.6, 10.2 Hz, 1 H), 4.51 (m, 1 H), 3.89 (t, J = 7.7 Hz, 2 H), 2.26–1.96 (m, 5 H), 1.24 (s, 3 H); ^{13}C NMR δ 133.8, 129.1, 77.7, 65.7, 53.3, 41.4, 34.4, 31.1, 26.6; IR (CCl_4) 2970, 2875, 1091, 1042; MS m/z 172 (M^+, 0.1), 159 (31), 157 (100), 137 (21), 121 (42), 93 (42), 91 (42), 55 (49), 43 (48).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.55; H, 7.44.

6-Chloro-3,3a,4,5,6,8a-hexahydro-(3aα,6β,8aα)-2*H*-cyclohepta[*b*]-furan (22). Method C was used on **2b** and gave **22** (88%, >98% cis): ^{1}H NMR δ 5.59 (app s, 2 H), 4.73 (m, 1 H), 4.64 (m, J_{AB} = 8.2 Hz, 1 H), 3.93 (app dt, J = 3.3, 8.7 Hz, 1 H), 3.60 (app dt, J = 6.5, 8.7 Hz, 1 H), 2.41 (m, 1 H), 2.15–2.01 (m, 3 H), 1.82–1.71 (m, 2 H), 1.63–1.48 (m, 1 H); ^{13}C NMR δ 131.3, 128.5, 78.7, 66.9, 59.0, 41.5, 34.2, 33.9, 26.2; IR (CCl_4) 2938, 2863, 1454, 1082, 1058; MS m/z 172 (M^+, 0.1), 137 (100), 83 (20), 67 (26), 55 (46), 41 (39), 39 (59).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.42; H, 7.50.

7-Chloro-2,3,4,4a,5,6,7,9a-octahydro-(4aα,7β,9aα)-cyclohepta[*b*]pyran (23). Method C was used on **4b** and gave **23** (81%, >98% cis): ^{1}H NMR δ 5.83 (ddd, J = 2.2, 3.6, 12.6 Hz, 1 H), 5.66 (ddd, J = 1.6, 3.9, 12.6 Hz, 1 H), 4.71 (m, 1 H), 4.40 (m, 1 H), 3.76 (ddd, J = 3.2, 8.5, 11.5 Hz, 1 H), 3.63 (m, 1 H), 2.19–1.95 (m, 4 H), 1.75–1.48 (m, 5 H); ^{13}C NMR δ 132.3, 131.6, 76.3, 64.5, 60.3, 37.8, 33.5, 27.5, 27.1, 24.9; IR (CCl_4) 2936, 2854, 1439, 1089, 1074; MS m/z 186 (M^+, 1.1), 151 (100), 97 (29), 91 (23), 71 (35), 41 (29).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.42; H, 7.50.

***trans*-6-Acetoxy-3,4,6,7,8,8a-hexahydro-2*H*-benzo[*b*]pyran (27).** Method A was used on **26** and gave **27** (60%, >98% trans): ^{1}H NMR δ 5.43 (br s, 1 H), 5.31 (m, 1 H), 3.98 (m, J_{AB} = 11.3 Hz, 1 H), 3.89 (m, 1 H), 3.55 (ddd, J = 3.4, 11.1, 11.3 Hz, 1 H), 2.39–2.20 (m, 2 H), 2.14–2.05 (m, 2 H), 2.04 (s, 3 H), 1.79–1.64 (m, 2 H), 1.61–1.47 (m, 2 H); ^{13}C NMR δ 170.7, 140.7, 121.5, 73.9, 69.6, 67.8, 31.5, 27.8, 27.1, 26.5, 21.3; IR ($CDCl_3$) 2947, 2850, 1728, 1366, 1249, 1206, 1084, 1022; MS m/z 196 (M^+, 0.2), 154 (10), 136 (100), 108 (34), 91 (16), 79 (22), 67 (20).

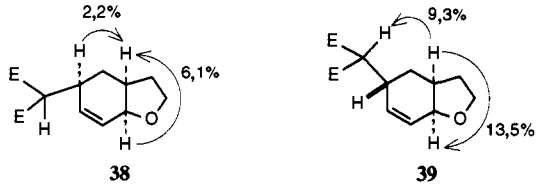


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Figure 1.

5-Methoxy-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (28). Method D was used on **2a** and gave **28** (75%, 91% cis): ^{1}H NMR δ 6.00 (ddd, J = 1.4, 2.7, 10.1 Hz, 1 H), 5.89 (ddd, J = 2.1, 3.5, 10.1 Hz, 1 H), 4.05 (m, 1 H), 4.00 (ddd, J = 6.9, 8.2, 8.6 Hz, 1 H), 3.80 (ddd, J = 5.4, 8.3, 8.5 Hz, 1 H), 3.76 (m, 1 H), 3.39 (s, 3 H), 2.33 (m, 1 H), 2.19 (m, 1 H), 1.95 (dddd, J = 1.4, 4.7, 4.9, 12.1 Hz, 1 H), 1.73 (m, 1 H), 1.33 (ddd, J = 10.2, 12.1, 12.3 Hz, 1 H); ^{13}C NMR δ 133.5, 126.5, 75.7, 74.1, 67.0, 55.8, 34.8, 32.6, 30.7.

5-Ethoxy-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (29). Method D was used on **2a** and gave **29** (85%, 91% cis): ^{1}H NMR δ 5.99 (ddd, J = 1.2, 1.4, 10.2 Hz, 1 H), 5.87 (ddd, J 2.0, 3.4, 10.2 Hz, 1 H), 4.05 (m, 1 H), 3.99 (app q, J = 7.7 Hz, 1 H), 3.84 (m, 1 H), 3.79 (dt, J = 5.2, 8.4 Hz, 1 H), 3.57 (q, J = 7.0 Hz, 2 H), 2.32 (m, 1 H), 2.18 (m, 1 H), 1.93 (ddt, J = 1.2, 4.8, 12.0 Hz, 1 H), 1.72 (m, 1 H), 1.35 (dt, J = 10.2, 12.2 Hz, 1 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 134.0, 126.3, 74.1, 74.0, 67.0, 63.5, 34.9, 32.7, 31.3, 15.6; IR (CCl_4) 2977, 2867, 1104, 1063; MS m/z 168 (M^+, 2.4), 123 (26), 114 (19), 96 (54), 78 (46), 55 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.42.

5-(Benzyloxy)-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (30). Method D was used on **2a** and gave **30** (75%, 91% cis): ^{1}H NMR δ 7.36–7.23 (m, 5 H), 6.05 (dd, J = 1.3, 10.1 Hz, 1 H), 5.89 (ddd, J = 2.0, 3.4, 10.1 Hz, 1 H), 4.59 (s, 2 H), 4.06–3.92 (m, 3 H), 3.79 (dt, J = 6.1, 8.4 Hz, 1 H), 2.31 (m, 1 H), 2.18 (m, 1 H), 1.97 (ddt, J = 1.2, 3.5, 12.1 Hz, 1 H), 1.73 (m, 1 H), 1.44 (dt, J = 10.1, 12.2 Hz, 1 H); ^{13}C NMR δ 138.5, 133.8, 128.3, 127.6, 127.5, 126.5, 74.0, 73.7, 70.0, 67.0, 34.9, 32.6, 31.2.

6-Ethoxy-3,4,4a,5,6,8a-hexahydro-(4aα,6β,8aα)-2*H*-benzo[*b*]pyran (31). Method D was used on **4a** and gave **31** (86%, >98% cis): ^{1}H NMR δ 5.95 (m, J_{AB} = 10.2 Hz, 1 H), 5.81 (ddd, J = 1.9, 4.8, 10.2 Hz, 1 H), 4.00–3.91 m, 2 H), 3.78 (m, 1 H), 3.61–3.51 (m, 2 H), 3.45 (m, 1 H), 1.96 (ddd, 9.9, 12.2, 12.6 Hz), 1.86–1.62 (m, 5 H), 1.35 (m, 1 H), 1.21 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 133.8, 128.1, 75.3, 71.5, 68.4, 63.1, 31.6, 29.0, 28.9, 21.8, 15.6; IR (CCl_4) 2931, 2842, 1107, 1091, 1067; MS m/z 182 (M^+, 55), 137 (44), 128 (31), 123 (45), 110 (100), 95 (57), 91 (36), 84 (79), 67 (54), 55 (87).

5-Ethoxy-2,2-dimethyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (32). Method D was used on **5** and gave **32** (83%, 91% cis): ^{1}H NMR δ 5.98 (m, J_{AB} = 10.2 Hz, 1 H), 5.87 (ddd, J = 2.0, 3.4, 10.2 Hz, 1 H), 4.20 (m, 1 H), 3.83 (m, 1 H), 3.56 (q, J = 7.0 Hz, 2 H), 2.31 (m, 1 H), 2.08 (dd, J = 8.6, 12.8 Hz, 1 H), 1.91 (m, J_{AB} = 12.8 Hz, 1 H), 1.58 (dd, J = 3.4, 12.6 Hz, 1 H), 1.49 (ddd, J = 10.0, 12.2, 12.6 Hz, 1 H), 1.34 (s, 3 H), 1.24 (s, 3 H), 1.22 (t, J = 7.0 Hz, 1 H); ^{13}C NMR δ 133.8, 126.7, 80.7, 74.4, 72.6, 63.5, 45.3, 36.3, 32.2, 30.2, 28.4, 15.6; IR (CCl_4) 2974, 2871, 1365, 1106, 1059; MS m/z 196 (M^+, 5), 151 (49), 124 (100), 123 (60), 109 (53), 98 (56), 95 (74), 43 (88).

5-Ethoxy-7a-methyl-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (33). Method D was used on **6** and gave **33** (55%, 87% cis): ^{1}H NMR δ 5.85 (ddd, J = 0.9, 2.4, 10.2 Hz, 1 H), 5.68 (dd, J = 1.8, 10.2 Hz, 1 H), 3.91–3.76 (m, 3 H), 3.56 (app dq, J = 1.9, 7.0 Hz, 2.22 (dd, J = 8.2, 12.1 Hz, 1 H), 2.07 (m, 1 H), 1.94–1.81 (m, 2 H), 1.61 (ddd, J = 8.0, 10.0, 12.8 Hz, 1 H), 1.22 (s, 3 H), 1.21 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 132.8, 129.7, 78.7, 72.7, 65.8, 63.7, 40.6, 31.8, 31.1, 26.8, 15.6; IR (CCl_4) 2974, 2930, 2872, 1446, 1370, 1089; MS m/z 182 (M^+, 4), 167 (38), 121 (91), 93 (35), 92 (100), 77 (23), 55 (53), 43 (89).

6-Methoxy-3,3a,4,5,6,8a-hexahydro-(3aα,6β,8aα)-2*H*-cyclohepta[*b*]-furan (34). Method D was used on **2b** and gave **34** (74% >98% cis): ^{1}H NMR δ 5.62 (m, J_{AB} = 10.3 Hz, 1 H), 5.53 (m, J_{AB} = 10.3 Hz, 1 H), 4.61 (m, J_{AB} = 8.8 Hz, 1 H), 3.98–3.83 (m, 2 H), 3.54 (app dt, J = 6.0, 7.8 Hz, 1 H), 3.35 (s, 3 H), 2.23 (m, 1 H), 2.09 (m, 1 H), 1.92 (m, 1 H), 1.63–1.37 (m, 4 H); ^{13}C NMR δ 129.9, 129.1, 79.6, 77.8, 66.7, 56.8, 39.2, 34.7, 29.0, 26.2.

6-Ethoxy-3,3a,4,5,6,8a-hexahydro-(3aα,6β,8aα)-2*H*-cyclohepta[*b*]-furan (35). Method D was used on **2b** and gave **35** (87%, >98% cis): ^{1}H NMR δ 5.62–5.49 (m, 2 H), 4.60 (m, J_{AB} = 8.3 Hz, 1 H), 4.02 (m, 1 H), 3.89 (app dt, J = 3.2, 8.5 Hz, 1 H), 3.62–3.39 (m, 3 H), 2.22 (m, 1 H), 2.07 (m, 1 H), 1.90 (m, 1 H), 1.62–1.37 (m, 4 H), 1.20 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 129.7, 129.5, 79.6, 76.1, 66.7, 64.4, 39.2, 34.7, 29.3, 26.3, 15.5; IR (CCl_4) 2977, 2940, 2862, 1112, 1098, 1084, 1059; MS m/z 182 (M^+, 1.6), 136 (36), 121 (21), 109 (41), 83 (49), 55 (52), 29 (100).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.23; H, 9.89.

6-(Benzyloxy)-3,3a,4,5,6,8a-hexahydro-(3aα,6β,8aα)-2*H*-cyclohepta-[*b*]furan (36). Method D was used on **2b** and gave **36** (85%, >98% cis): ^{1}H NMR δ 7.38–7.27 (m, 5 H), 5.63 (app s, 2 H), 4.64–4.46 (m, 3 H), 4.13 (m, 1 H), 3.90 (app dt, J = 3.0, 8.7 Hz, 1 H), 3.53 (app dt, J = 6.1, 8.7 Hz, 1 H), 2.18 (m, 1 H), 2.08 (m, 1 H), 1.93 (m, 1 H), 1.67–1.55 (m, 3 H), 1.50–1.38 (m, 1 H); ^{13}C NMR δ 138.3, 129.9, 129.3, 128.3, 127.6, 127.5, 79.6, 75.6, 70.9, 66.7, 39.2, 34.7, 29.3, 26.2; IR (CCl_4) 3033, 2940, 2861, 1454, 1086, 1062; MS m/z 244 (M^+, 0.2%), 153 (12), 138 (18), 109 (32), 91 (100), 55 (36). IR (CCl_4) 3034, 2943, 2863, 1064, 1028; MS m/z 230 (M^+, 0.3), 200 (7), 124 (11), 91 (100), 78 (16), 65 (21), 55 (31).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.86; H, 8.44.

7-Ethoxy-2,3,4,4a,5,6,7,9a-octahydro-(4aα,7β,9aα)-cyclohepta[*b*]-pyran (37). Method D was used on **4b** and gave **37** (85%, >98% cis): ^{1}H NMR δ 5.78 (app ddt, J = 1.0, 2.6, 12.7 Hz, 1 H), 5.56 (app dtd, J = 0.8, 2.5, 12.7 Hz, 1 H), 4.42 (m, 1 H), 3.89 (m, 1 H), 3.73 (ddd, J = 4.6, 8.5, 11.6 Hz, 1 H), 3.63 (dtd, J = 0.9, 4.2, 11.6, 1 H), 3.55–3.45 (m, 2 H), 2.02 (m, 1 H), 1.93–1.54 (m, 7 H), 1.44 (m, 1 H), 1.21 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 134.3, 129.9, 78.7, 77.5, 63.9, 63.3, 36.9, 28.2, 28.0, 25.72, 25.67, 15.5; IR (CCl_4) 2930, 2855, 1440, 1392, 1100, 1073; MS m/z 196 (M^+, 12), 150 (76), 123 (49), 97 (100), 83 (61), 55 (85), 41 (91).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.20; H, 10.24.

5-(Dicarbomethoxymethyl)-2,3,3a,4,5,7a-hexahydro-(3aα,5β,7aα)-benzofuran (38). A solution of sodium dimethyl malonate in THF (4.7 mL of a 0.125 M solution, 0.58 mmol; prepared from 1.05 equiv of dimethyl malonate and 1.00 equiv of sodium hydride) was added to a mixture of **18** (84 mg, 0.53 mmol), $Pd(OAc)_2$ (2.6 mg, 0.000 12 mmol), and PPh_3 (12 mg, 0.000 48 mmol) under an atmosphere of nitrogen at 20 °C. After the mixture was stirred for 1 h at room temperature, saturated aqueous $NaHCO_3$ (2 mL), H_2O (1 mL), and ether (5 mL) were added. The layers were separated, and the aqueous phase was extracted with ether (3 × 5 mL). The combined ethereal phases were washed with brine (2 mL) and dried ($MgSO_4$). The solvents were evaporated on a rotary evaporator, and the resulting oil was chromatographed on silica to give **38** (132 mg, 98%): ^{1}H NMR δ 5.98 (ddd, J = 2.7, 3.8, 10.0 Hz, 1 H), 5.79 (m, J_{AB} = 10.0 Hz, 1 H), 4.02–3.92 (m, 2 H), 3.80–3.71 (m, 1 H), 3.75 (s, 6 H), 3.29 (d, J = 9.2 Hz, 1 H), 2.82 (m, 1 H), 2.35–2.05 (m, 2 H), 1.68–1.57 (m, 2 H), 1.11 (app q, J = 12.2 Hz, 1 H); ^{13}C NMR δ 168.7, 168.6, 132.5, 127.0, 73.8, 66.5, 56.0, 52.5, 36.3, 36.0, 32.7, 29.8; IR (CCl_4) 2953, 1760, 1741, 1435, 1239, 1155; MS (direct inlet) m/z 209 (3), 177 (3), 123 (24), 122 (100), 121 (15), 91 (20).

The stereochemistry of **38** was established by NOE experiments (Figure 1).

5-(Dicarbomethoxymethyl)-2,3,3a,4,5,7a-hexahydro-(3aα,5α,7aα)-benzofuran (39). NaH (36 mg, 1.21 mmol) was added to a solution of dimethyl malonate (160 mg, 1.21 mmol) in THF (10 mL). After the mixture was stirred for 0.5 h at room temperature, the solvent was evaporated in vacuo, and acetonitrile (6 mL) was added. A solution of **18** (96 mg, 0.61 mmol) in acetonitrile (4 mL) was added, and the reaction mixture was heated to reflux under an atmosphere of nitrogen for 20 h. The mixture was allowed to cool to room temperature, and H_2O (5 mL) was added. This solution was extracted with ether (4 × 7 mL), and the combined ethereal phases were washed with brine (2 mL) and dried ($MgSO_4$). The solvent was evaporated, and the resulting oil was chromatographed on silica to give **39** (150 mg, 97%): ^{1}H NMR δ 5.83 (br s, 2 H), 4.20 (d, J = 6.6 Hz, 1 H), 3.91 (ddd, J = 5.3, 8.1, 8.3 Hz, 3.80–3.71 (ddd, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.31 (d, J = 9.8 Hz, 1 H), 2.97 (m, 1 H), 2.43 (m, 1 H), 2.06 (m, 1 H), 1.78–1.65 (m, 2 H), 1.58 (ddd, J = 5.4, 6.6, 12.7 Hz, 1 H); ^{13}C NMR δ 168.6, 168.5, 130.4, 128.9, 73.8, 66.5, 55.7, 52.6, 33.7, 32.6, 30.5, 27.9; IR (CCl_4) 2953, 1760, 1740, 1435, 1242, 1160; MS (direct inlet) m/z 209 (5), 177 (3), 123 (25), 122 (100), 121 (19), 91 (17).

The stereochemistry of **39** was established by NOE experiments (Figure 1).

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141612-33-1; **5**, 141612-34-2; **6**, 141612-35-3; **7**, 141612-36-4; **8**, 141612-37-5; **9**, 141612-38-6; **10**, 141612-39-7; **11**, 141612-40-0; **12**, 141612-41-1; **13**, 141612-42-2; **14**, 141612-43-3; **15**, 141723-94-6; **16**, 141612-44-4; **17**, 141723-95-7; **18**, 141612-45-5; **19**, 141612-46-6; **20**, 141612-47-7; **21**, 141612-48-8; **22**, 141612-49-9; **23**, 141612-50-2; **26**, 141612-51-3; **27**, 141612-52-4; *cis*-**28**, 141612-53-5; *trans*-**28**, 141612-54-6; *cis*-**29**, 141612-55-7; *trans*-**29**, 141612-56-8; *cis*-**30**, 141612-57-9; *trans*-**30**, 141612-58-0; **31**, 141612-59-1; *cis*-**32**, 141612-60-4; *trans*-**32**, 141612-61-5; *cis*-**33**, 141612-62-6; *trans*-**33**, 141612-63-7; **34**, 141612-64-8; **35**, 141612-65-9; **36**, 141612-66-0; **37**, 141612-67-1; **38**, 141612-68-2; **39**, 141612-69-3; dimethyl malonate, 108-59-8; palladium acetate, 3375-31-3.

Dependence of Metal Ion Complexation and Intermolecular Aggregation on Photoinduced Geometric Isomerism in a Crown Ether Styryl Dye

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Abstract: Photoisomerization and complexation with alkaline-earth metal cations of a 2-[2-(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-16-yl)ethenyl]-3-(3-sulfopropyl)benzothiazolium betaine has been studied by steady-state and time-resolved electronic spectroscopy. The dye is highly sensitive to complexed metal cations, showing characteristic hypsochromic shifts of the long wavelength absorption and fluorescence bands, as well as a decrease in the fluorescence quantum yield upon complexation. The stabilities of the complexes are drastically changed by photoisomerization, with enhanced stability of the cis ligand complex being attributed to the intramolecular interaction of the complexed cation with a tethered sulfonate anion. This intramolecular capping also induces a strong hypsochromic shift of up to 70 nm from the absorption maximum of the uncapped trans ligand complex. Unlike this capped cis complex, the uncapped trans complex is partially aggregated, even at low concentration, as a result of the association of the sulfonate anion of one dye with the "crowned" cation of a second molecule. At high metal ion concentrations, the aggregates dissociate as the sulfonate group becomes associated with a free metal cation. Similar interactions are also responsible for the relaxation of the anion-capped cis complex to its "uncapped" form at high cation concentrations.

Introduction

Chromoionophoric macrocycles are interesting primarily because of their utility in the identification and quantitative determination of metal cations.[1-3] Since cation binding is sensitive to the ligand environment, the binding equilibrium constant can be effectively controlled by employing a switch-functionalized system where a crown ether is bound intramolecularly to an antenna moiety which is responsive to an external stimulus.[4] Various responsive crown ethers have been synthesized for dynamic control of cation binding induced by changes in pH, redox potential, temperature, magnetic field, light, etc.[4,5] Photoresponsive systems are often most useful, especially if the photoexcitation causes a structural change in the antenna, e.g., photoisomerization.[4-6]

An additional method to control cation binding occurs in crown ethers bearing a tethered photoresponsive anionic cap.[4] The anionic group acts cooperatively with the crown ring: thus, the cation binding ability is altered by changing the proximity of this group, e.g., by photoisomerization. The different stabilities of capped and uncapped metal–crown ether complexes can be used for photoresponsive ion extraction and light-driven ion transport across membranes.[6]

Thus far, most studies of photoresponsive crown ethers have involved azobenzene derivatives,[3,4,7] although several reports on stilbene derivatives have also appeared.[8,9] Recently, the syntheses of styryl dyes containing heteroaromatic residues and of various crown-ether groups bearing O,N,S heteroatoms in different combinations have been reported.[10-14] These dyes are intensively colored and show significant hypsochromic shifts upon complexation with alkali- or alkaline-earth metal cations. High quantum yields for trans-to-cis and cis-to-trans photoisomerization are observed for each species investigated. Zwitterionic crown ether styryl dyes bearing a photoresponsive anionic cap have also been prepared.[11]

In this paper, we report a study of the photoisomerization and complexation of alkaline-earth metal cations with a 2-[2-(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-16-yl)ethenyl]-3-(3-sulfopropyl)benzothiazolium betaine (L, Figure 1) by steady-state and time-resolved electronic spectroscopy. Our results indicate high sensitivity of the dye to

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