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Selective Mixed Tishchenko Reaction via Substituted 1,3-Dioxan-4-ols

Olli P. Törmäkangas,[†] Pauli Saarenketo,[‡,§] and Ari M. P. Koskinen*[,†]

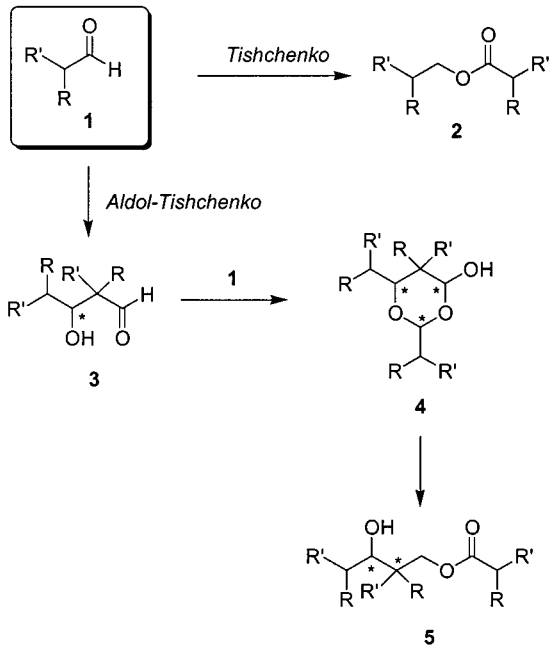
Laboratory of Organic Chemistry, Helsinki University of Technology, P.O. Box 6100, FIN-02015 HUT, Finland, and Department of Chemistry, University of Jyväskylä, Survontie 9, FIN-40351 Jyväskylä, Finland

Abstract:

Monoesters of 1,3-diols can be prepared with the mixed Tishchenko reaction from β-hydroxy aldehydes and another aldehyde. These two aldehydes form a diastereomeric mixture of 1,3-dioxan-4-ol hemiacetal derivatives which can be further converted to monoesters with suitable catalysts. Limitations in the formation and esterification of this hemiacetal intermediate have been investigated in this work and the formation and stability of 1,3-dioxan-4-ols was found to be aldehyde-, temperature-, and solvent-dependent. A new method was developed for selective preparation of monoesters of 1,3-diols with this mixed Tishchenko reaction via 1,3-dioxan-4-ols without any significant side products. During the development of this method a possibility to scale up the reactions to reach a selective and economical process was one of the main targets in this work.

The conventional Tishchenko reaction of aldehydes gives simple esters with moderate-to-excellent yield (Scheme 1; **1**→**2**)[1] typically in the presence of Lewis acidic catalysts such as aluminium alcoholates.[2] Several Lewis acidic transition metal complexes have also been found effective.[3] For enolizable aldehydes, sequential aldol−Tishchenko reaction can become competing if the catalyst is sufficiently basic (Scheme 1; **1**→**3**→**5**).[4] The basic catalyst first accomplishes the aldol reaction which is followed by Tishchenko esterification by the Lewis acidic nature of the same catalyst. In the mixed Tishchenko reaction between different aldehydes the product distribution is difficult to control.[5] 1,3-Dioxan-4-ols **4** have been reported as reaction intermediates in the homoaldol−Tishchenko reaction (Scheme 1) with only one enolizable aldehyde.[6] Dioxanol **4** type intermediates react further to the monoester **5**. In other reports the formation of **4** has not been disclosed, but a direct Tishchenko step (**3**→**5**) via a [6,6]-membered bicyclic transition state has been suggested.[7]

Scheme 1. **Tishchenko and homoaldol−Tishchenko reactions with enolizable aldehydes**



Our interest in this topic was originally triggered by the potential versatility of the mixed aldol−Tishchenko reaction and the possible applications of mixed esters in more complex natural product syntheses where the target molecules bear monoester moieties of diols (e.g., polyketides). However, the most important application of 1,3-diol monoesters is their use as the most common coalescing agents in the paint and coating industry, and this was also the main focus of our work.[8] Herein we report our results on the formation and stability of the mixed 1,3-dioxan-4-ols of type **8** and their further esterification to a variety of 1,3-diol monoesters.

* To whom correspondence may be sent. Telephone: +358 9 451 2526. Fax: +358 9 451 2538. E-mail: ari.koskinen@hut.fi.

[†] Helsinki University of Technology.

[‡] University of Jyväskylä.

[§] X-ray crystal structure analysis.

(1) (a) Tischtschenko, W. *J. Russ. Phys. Chem.* **1906**, *38*, 355, 482. (b) Tischtschenko, W. E. *Chem. Zentr.* **1906**, *77*, I, 1309, 1554, 1556. For mechanism, see: (c) Ogata, Y.; Kawasaki, A.; Kishi, I. *Tetrahedron* **1967**, *23*, 825−830.

(2) (a) Ogata, Y.; Kawasaki, A. *Tetrahedron* **1969**, *25*, 2845−2851. (b) Saegusa, T.; Hirota, K.; Hirasawa, E.; Fujii, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 967−972. (c) Child, W. C.; Adkins, H. *J. Am. Chem. Soc.* **1923**, *45*, 3013−3023. Fast Tishchenko reaction has been reported recently with bidentate aluminum alcoholate catalysts: (a) Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 7695−7698.

(3) (a) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885−3891. (b) Ito, T.; Horino, H.; Koshiro, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504−512.

(4) (a) Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1947**, *69*, 2605−2607. (b) Kuplinski, M. S.; Nord, F. F. *J. Org. Chem.* **1943**, *8*, 256−270.

(5) (a) Ogata, Y.; Kawasaki, A. *Tetrahedron* **1969**, *25*, 929−935. (b) Lin, I.; Day, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 5133−5135. (c) For transition metal-catalyzed crossed Tishchenko reaction, see: Morita, K.-I.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748−3752.

(6) (a) Törmäkangas, O. P.; Koskinen, A. M. P. *Org. Process Res. Dev.* **2001**, *5* (4), 421−425. (b) Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1946**, *68*, 1674−1675.

(7) (a) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427−1429. (b) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674−5675. (c) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 3409−3412.

(8) Kirk, R. E.; Othmer, D. F. *Encyclopedia of Chemical Technology*, 3rd ed.; Wiley-Interscience: New York, 1984; Vol. 11, p 966−967.

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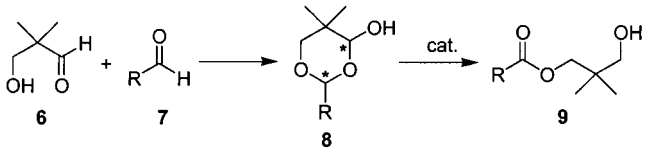
Scheme 2. **Aldol−Tishchenko type-mixed Tishchenko reaction**



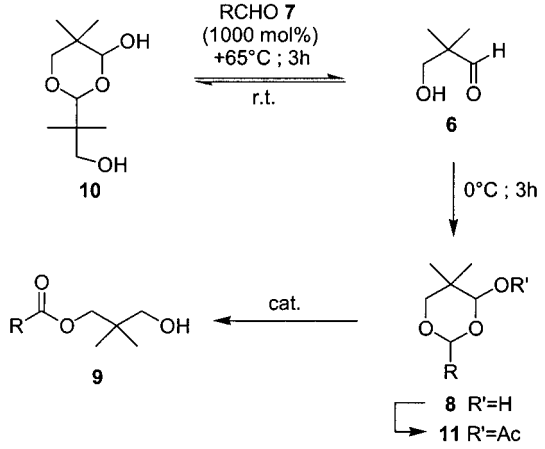
Results and Discussion

The purpose of our studies was to gain insight into the formation and properties of mixed dioxanols **8** as well as to develop a selective process where their Tishchenko reaction to 1,3-diol monoesters takes place while competing reactions are avoided.[9] One goal was to create an economically and environmentally advantageous process which would be possible to scale up to industrial scale without any hazardous or expensive steps. However, the work reported in this paper describes the main features of the method including the possibilities and the limitations. For synthetic versatility, differing from typical aldol−Tishchenko reactions, a mixed aldol−Tishchenko reaction was investigated (Scheme 2).

The Tishchenko reaction of 1,3-dioxan-4-ols has been reported typically for dimeric aldol products.[10] Mixed dimers from a β-hydroxyaldehyde and a second aldehyde have been suspected for instability, but detailed investigations on their esterification have not been reported.[11] Very little is known about the effects of different substituents on the formation, stability, stereochemistry, and reactivity of dioxanols similar to **8**. 2,2-Dimethyl-3-hydroxypropanal **6** (3-hydroxypivaladehyde [HPA])[12] was chosen as the starting material because of its stability and easy detection. Aldehyde **6** was isolated as the dimer **10**, which by ^{1}H NMR ($CDCl_3$) was a mixture of diastereomers in 60:40 ratio (Scheme 3). By ^{1}H NMR in D_2O, at room temperature the equilibrium consisted of 56% **6** and 44% **10**, and at 35 °C, the equilibrium rapidly shifted completely to monomer **6**. In contrast, in $CDCl_3$ at 35 °C only 9% was in monomeric form, and heating at 50 °C for 90 min was required to shift equilibrium to monomer **6**. Slow dimerisation of **6** was observed in $CDCl_3$ when the solution was cooled back to room temperature.

We next optimized the reaction conditions and requirements for preparation of mixed dimers. The first "mixed" dioxanol **8** we tried to prepare was the dimer of **6** and 2-methylpropanal **7b**. In our normal procedure to produce

Scheme 3. **Preparation of monoesters of 1,3-diols with mixed Tishchenko reaction via 1,3-dioxan-4-ol intermediates**



new "mixed" 1,3-dioxan-4-ols dimeric, **10** was first monomerized in the presence of a large excess (10 mol equiv) of **7b** by heating at 65 °C without solvent (Scheme 3). At higher temperatures **6** started to decompose via retro-aldol reaction. Heating (monomerisation) should be continued for at least 3 h at 65 °C to monomerize all the dimeric **10**. When the solution was cooled to room temperature, slow formation of **8b** was observed, and a stable equilibrium was reached only in 2.5−3 days, and monomer **6** was still present (^{1}H NMR in $CDCl_3$). When the cooling was repeated at 0 °C, the formation of dioxanol **8** was already complete in less than 3 h, and only a trace of monomeric **6** was observed with ^{1}H NMR. The product mixture contained the desired dimer **8b**, dimer **10**, free aldehyde **7**, and sometimes a trace of monomeric **6**.[13]

The role of the free aldehyde **7** was also studied to uncover its effect on the stereochemistry and the rate of formation of dioxanols **8** (Table 1). Both steric and electronic effects of the aldehydes **7** were studied by varying the substituents R to obtain a mixture of diastereomers of compounds **8a**−**f**. All dimers were prepared with the method described above. The product distribution was measured directly after step **6**→**8** by ^{1}H NMR. Due to the vulnerability of the products to decomposition, the product mixture was acetylated or esterified directly to the corresponding monoesters **9** for further analysis.

The two dioxanol diastereomers formed in practically identical ratios regardless of the substituent R. The identity of the cis/trans isomers was secured through an X-ray crystallographic analysis of the crystalline major diastereomer of **8c**, separable by careful chromatography and crystallisation from MeOH:H_2O. Dimer **10** is rather stable even at room temperature, and there are no problems in isolation and storing, but most of the dioxanols **8** prepared here were found to be relatively unstable. The reason for the better stability of dimer **10** compared to that of **8** was studied by means of molecular modelling. The calculations (MacroModel 6.0; Monte Carlo, solvent $CDCl_3$) gave some evidence for the possibility of intramolecular hydrogen bonding in the dimeric

(9) **Aldol reaction**: (a) Casiraghi, C.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972. (b) Machajewski, T. D.; Wong, C.-H.; Lerner, R. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (d) Cowden, C.; Paterson, I. *Org. React.* **1997**, *51*, 1−200. (e) Sawamura, M.; Ito, Y. *Catal. Asymmetric Synth.* **1993**, 367−388. (f) Bednarski, M. D. *Appl. Biocatal.* **1991**, *1*, 87−116. **Cannizzaro reaction**: (g) Kharasch, M. S.; Snyder, R. H. *J. Org. Chem.* **1949**, *14*, 819−835. (h) Pfeil, E. *Ber.* **1951**, *84*, 229−45. **Meerwein−Ponndorf−Verley reduction/Oppenauer oxidation**: (i) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007−1017. (j) Pickart, D. E.; Hancock, C. K. *J. Am. Chem. Soc.* **1955**, *77*, 4642−4643. **Tollens reaction**: (k) March, J. *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: 1993; p 955.

(10) Fouquet, G.; Merger, F.; Platz, R. *Liebigs Ann. Chem.* **1979**, *46*, 1591−1601.

(11) Späth, E.; Szilâgui, I. v. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 949−956.

(12) Merger, F.; Platz, R.; Fuchs, W. (Badische Anilin- und Soda-Fabrik A.-G.). Ger. Offen. Pat. 1957301, 1971; *Chem. Abstr.* **1971**, *75*, 76165b.

(13) Similar results have been obtained under rather vigorous reaction conditions (8 h, 160 °C, under 3.5 MPa pressure): Duke, R. B.; Perry, M. A. (Eastman Kodak Company). FR Pat. 1414216, 1964; *Chem. Abstr.* **1966**, *64*, 11090c.

Table 1. **Product distribution for the preparation of new dimers**

entry		aldehyde **7**	R	**6** (mol %)[a]	**8** (mol %)[a,b] *trans*	**8** (mol %)[a,b] *cis*	**10** (mol %)[a] (diastereomers)
1	a	propanal	Et	0	22	48	30 (40:60)
2	b	2-methylpropanal	*i*-Pr	0	25	50	25 (41:59)
3	c	pivalaldehyde	*t*-Bu	0	32	60	8 (40:60)
4	d	2-ethylhexanal	1′-Et-pentyl	0	38	49	13 (31:69)
5	e	crotonaldehyde	$CH{=}CHCH_3$	62	0	0	38 (41:59)
6	f	benzaldehyde	Ph	51	42	58	34 (40:60)
7	g	cyclohexylcarboxaldehyde	C_6H_{11}	0	34	66	18 (40:60)

[a] The product distribution was determined by ^{1}H NMR. [b] Relative stereochemistry has been detemined by X-ray crystallography of acetylated **8c**.

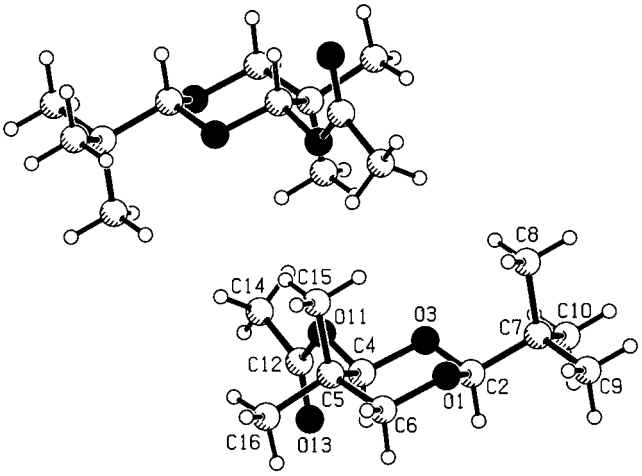


Figure 1. **X-ray structure of the *cis*-enantiomers of 4-acetoxy-5,5-dimethyl-2-*tert*-butyl-1,3-dioxane 8c, crystallized in a centrosymmetric space group *P*-1. Unit cell contained both enantiomers of 8c which are shown in the figure.**

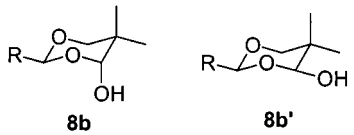


Figure 2.

β-hydroxyl aldehydes between oxygen at ring position 1 and the hydroxyl group in the side chain at ring position 2. Also, the differences in calculated minimum energies between the diastereomers were compared to the ratio of diastereomers obtained with NMR. In the case of dioxanol **8b** the calculations gave the axial anomers **8b** the energy minimum of $\Delta G = -177.6$ kJ, and for the equatorial anomers **8b′** $\Delta G = -166.7$ kJ, corresponding to a ratio of 80:20, in good agreement with the observed ratio 73:27. After the formation of the new dioxanal-type mixed dimer, the 2-methylpropanal (**7b**) excess was removed under reduced pressure (0.1 mmHg) at 0 °C. The product distribution was followed with ^{1}H NMR during the evaporation, and the new dimer **8b** was observed to slowly decompose. The reaction was found to be limited to low-boiling aldehydes **7**. With higher-boiling aldehydes such as 2-ethylhexanal (**7d**) the reaction had to be heated to room temperature (under reduced pressure of 0.1 mmHg) to evacuate an excess of free aldehyde. This caused significant decomposition of dioxanol **8d**. The effect of the solvent on the stability of mixed dimer **8b** was studied by ^{1}H NMR. Dioxanol **8b** was prepared at 0 °C, dissolved

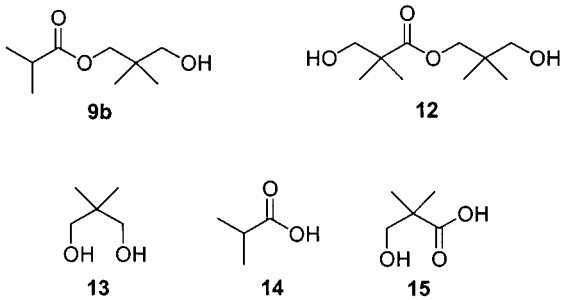


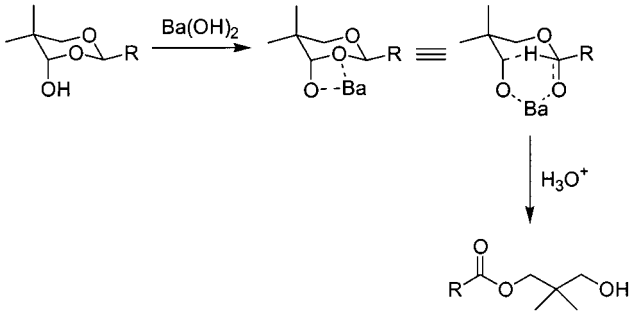
Figure 3.

in different deuterated solvents. The decomposition was followed as a function of time at room temperature. After 3 days **8b** was partly decomposed in d_6-benzene (33%) and $CDCl_3$ (61%). On the other hand, in d_6-DMSO the decomposition was not observed (<1%). The reason for this is believed to be the hydrogen bonding between the hydroxyl group of the dioxanol and DMSO which stabilizes the acetal-type dioxanol structure.

In our earlier studies we have shown that the catalyst in the Tishchenko esterification of such dimers should bear sufficient basicity to deprotonate the hydroxyl proton and Lewis acidity for the intramolecular hydride shift from ring position 2 to position 4.[6a,14] Esterification of dioxanol **8b** to the corresponding monoester **9** (R = *i*-Pr) was first carried out with 30−40 mol % of traditional metal hydroxide catalysts such as LiOH (4.55 M) or $Ba(OH)_2{\cdot}H_2O$ with low isolated yield (0−35%). Monoester **12** was formed with Tishchenko esterification of **10** (formed due to equilibration, Scheme 3). Products **13**, **14**, and **15** were formed by irreversible hydrolysis of monoesters **9b** and **12**. Use of 1,3-diol-based alkali metal monoalcoholates as catalysts was then investigated.[14a] Gratifyingly, the esterification of dioxanol **8b** occurred almost quantitatively in the presence of 30 mol % of 0.1 M solution (in THF) of monolithium alcoholate of diol **13**. Monoester **9b** was obtained in 86% isolated yield after 50 min. Monoesters **9a** and **9c** were obtained with the similar manner in 41 and 60% isolated yield, respectively. However, these two latter experiments were carried in several-times-smaller scales. The reaction was quenched with the addition of a catalytic amount of 2 M HCl to avoid side reactions during the workup. In larger scale the products can be isolated by fractional distillation under reduced pressure

(14) (a) Törmäkangas, O. P.; Koskinen, A. M. P. *Tetrahedron Lett.* **2001**, *42*, 2743−2746. (b) See also: Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954−2960.

Scheme 4



after workup. In these experiments (10 mmol of monomeric HPA) column chromatography was the preferred method for purification.

Tishchenko esterifications have also been studied previously with milder catalysts yielding the 1,3-diol monoester with excellent *anti*-selectivity, high yields and without any side reactions.[15] However, we found SmI_2 alone to be ineffective in the esterification of 1,3-dioxan-4-ols due to its low basic nature.

It has been claimed by Merger et al. that β-hydroxy aldehydes form both an acyclic hemiacetal and a cyclic 1,3-dioxan-4-ol and that these react to the corresponding diol monoester.[10] We found no evidence of such an open-ring hemiacetal by ^{1}H NMR. We believe that in the case of 1,3-dioxan-4-ols the metal first coordinates to the hydroxyl group and to the ring oxygen at position 3 which activates the hydride shift from ring carbon 2 to carbon 4. The reaction mixture was also acetylated, and no traces of open-ring forms were observed. However, the final stages of the mechanism are believed to be similar to the mechanism reported in the case of β-hydroxyketone and simple aldehyde in the presence of SmI_2.[15]

Conclusions

The formation of 1,3-dioxan-4-ol type acetal between a β-hydroxyaldehyde and a second aldehyde was shown to be especially temperature-dependent. This also explains the need for low reaction temperature in the case of Evans−Tishchenko and aldol−Tishchenko reactions. At 0 °C and in the presence of excess monofunctional aldehyde all the monomeric β-hydroxyaldehyde dimerized in 3 h to a diastereomeric mixture of 1,3-dioxan-4-ols. Also, the electronic effects of the aldehyde **7** were found to be important, for example, in the case of electron-withdrawing substituent R (crotonaldehyde) the formation of the initial hemiacetal is disfavored. With donor substituents (alkyl) the formation of dioxanols **8** is favored. Several dioxanol-type "mixed" dimers are rather unstable and sometimes even impossible to purify, and protection of the ring hydroxyl group may be needed for isolation and purification. The structure can be stabilized by intramolecular hydrogen bonding in the case of dimeric β-hydroxy aldehydes. The Tishchenko esterification can be favourably carried out in the presence of 1,3-diol-based monoalcoholate catalysts consistently giving high yields. Thus, excess aldehyde has to be evaporated before addition of the catalyst to avoid unfavorable and exothermic side reactions such as homo aldol−Tishchenko. The evaporated aldehyde can be recycled directly to the next batch. Furthermore, the process developed is possible to scale up to large (industrial) scale. However, this paper focused on the main features of the method, and the largest scale was the 10-mmol scale. The scale-up work to larger (possibly to pilot) has not been carried out yet. In industrial scale a possible need for cryogenic condenser cooling would raise the total costs of the method considerably. Finally, in comparison to alternative methods this is the most inexpensive way to prepare 1,3-dioxan-4-ols[16] and, further, 1,3-diol monoesters.[13] The method developed allows a design and preparation of various monoesters to be used as the coalescing agents for different purposes.

Experimental Section

All aldehydes were purchased from commercial sources (Aldrich) but (except formalin) were further distilled (purity >99.5%). TLC was performed on Merck silica gel 60-F plates staining with 1% anisaldehyde in acidic ethanol solution. Flash chromatography was performed on Merck silica gel 60 (230−400 mesh). NMR spectra were recorded on Bruker AM-200 and Varian Gemini 400 or Bruker DPX 400 instruments. $CDCl_3$ was filtered through basic alumina right before use to remove traces of HCl. Mass spectra were recorded on a Kratos MS80 RF Autoconsole instrument. All melting points were measured with Gallenkamp GMP (capillary) apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer Spectrum One apparatus. Perkin-Elmer 8420 gas chromatograph was used with OV-1701 silica column. The 4-hydroxy-1,3-dioxane derivatives **8** were very unstable and decomposed during flash chromatography, distillation under atmospheric and reduced pressure and even when kept under reduced pressure. The derivatives were identified directly from the product mixture with ^{1}H NMR and usually protected at the free hydroxyl group. In the following Experimental Section the dioxanols were first prepared and analyzed as a mixture followed by possible acetylation or direct Tishchenko esterification to monoesters and purification by means of column chromatography.

5,5-Dimethyl-4-hydroxyl-2-(1′,1′-dimethyl-2′-hydroxylethyl)-1,3-dioxane (10). Triethylamine (5.06 mL, 50 mmol) and formaldehyde (37.4 mL, 500 mmol, 10 mol equiv, 37% aqueous solution) were placed into a reaction vessel kept under argon. Isobutyraldehyde **7b** (45.4 mL, 500 mmol, 10 mol equiv) was added dropwise (over 10 min), and the temperature was raised to +75 °C. The reaction was stirred at +75 °C for 1 h and then cooled to room temperature. A white precipitate started to form at +45 °C. Isooctane (10 mL) was added, and the product was allowed to crystallise

(15) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449. See also: (b) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843−853.

(16) Alternative ways to produce 1,3-dioxan-4-ols: (a) Reduction of 1,3-dioxan-4-ones: Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) *m*-CPBA oxidation of cyclic vinyl ethers (1,3-dioxane type acetals): Wattenbach, C.; Maurer, M.; Frauenrath, H. *Synlett* **1999**, 303−306. (c) Treatment of acrolein in the presence of $TiCl_4$-*n*-Bu_4NI and 2 equiv of aldehyde: Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1* (9), 1383−1385.

overnight at room temperature. The white solid was filtered and triturated with isooctane. The product was filtered again, washed with 8 × 50 mL of cold isooctane, and dried to give **10** (44.4 g, 87%) as a mixture of diastereomers.[17] TLC: R_f = 0.39 (EtOAc:hexanes, 7:3). ^{1}H NMR ($CDCl_3$, 200 MHz) (Diastereomer 1, 40%) δ 4.91 (s, 1H), 4.81 (d, 1H, ^4J = 1.1 Hz), 3.85 (d, 1H, ^2J = 11.1 Hz), 3.46 (s, 2H), 3.39 (dd, 1H, ^2J = 11.1 Hz, ^4J = 1.1 Hz), 1.17 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.82 (s, 3H). (Diastereomer 2, 60%) δ 4.60 (s, 1H), 4.42 (s, 1H), 3.62 (d, 1H, ^2J = 11.4 Hz), 3.49 (s, 2H), 3.30 (dd, 1H, ^4J = 11.4 Hz, $^4J \approx$ 0.1 Hz), 1.06 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H). CI-MS (monomer when ionized with NH_3) 120 (M + 1 + NH_3), 72, 56, 41, 39.

5,5-Dimethyl-4-hydroxyl-2-isopropyl-1,3-dioxane (8b). Dimer **10** (1.022 g, 5.0 mmol) was dissolved in isobutyraldehyde **7b** (4.54 mL, 50 mmol, 1000 mol equiv) under Ar. The colourless solution was stirred for 3 h at +65 °C (±3 °C) to monomerize **6**. The solution was cooled to 0 °C and stirred for another 3 h. Excess **7b** was evaporated at 0 °C (60 min at 0.1 mmHg), yielding an oily product. TLC: R_f = 0.59 (EtOAc:hexane, 8:2). ^{1}H NMR ($CDCl_3$, 200 MHz) (*trans*-isomer 2*S**,4*S**-**8b**, 27%) δ 4.86 (d, 1H, OCH(*i*-Pr)O, ^3J = 4.4 Hz), 4.82 (d, 1H, −OCHOH, $^4J \approx$ 1 Hz), 3.89 (d, 1H, OCH_2C, ^2J = 11.0 Hz), 3.40 (d−d, 1H, OCH_2C, ^2J = 11.0 Hz, ^4J = 1.3 Hz), 1.76 (dq, 1H, $-CHMe_2$, ^3J = 7.0 Hz, ^3J = 4.4 Hz), 1.21 (s, 3H, ring CH_3), 0.94 (d, 6H, 2× (*i*-Pr) CH_3, ^3J = 7.0 Hz), 0.82 (s, 3H, ring CH_3). (*cis*-Isomer 2*S**,4*R**-**8b**, 73%) δ 4.60 (s, 1H, OCHOH), 4.36 (d, 1H, OCH(*i*-Pr)O, ^3J = 4.6 Hz), 3.60 (d, 1H, OCH_2C, ^2J = 11.5 Hz), 3.35 (d, 1H, OCH_2C, ^2J = 10.9 Hz), 1.87 (dq, 1H, $-CHMe_2$, ^3J = 6.9 Hz, ^3J = 4.6 Hz), 1.18 (s, 3H), 0.97 (d, 6H, 2× (*i*-Pr) CH_3, ^3J = 6.9 Hz), 0.83 (s, 3H, ring CH_3). The compound decomposed on CI-MS analysis.

4-Acetoxy-5,5-dimethyl-2-isopropyl-1,3-dioxane (11b). The product mixture (**8b**, 100 mol %) from above was cooled to 0 °C under argon. Pyridine (8.09 mL, 100 mmol, 1000 mol equiv) and freshly distilled acetic anhydride (9.44 mL, 100 mmol, 1000 mol equiv) were added, and the solution was stirred at 0 °C for 4 h and then allowed to warm to room temperature overnight. Excess pyridine was removed by evaporation with toluene (3 × 20 mL). Salts were removed with filtration through a silica column (height 15 cm, diameter 3 cm) with EtOAc. After evaporation the crude product mixture was purified with column chromatography (CH_2Cl_2:hexane, 80:20), and a mixture of diastereomers (ratio 26:74) of **11b** was obtained in 44% overall yield (starting from **11**) (0.949 g). TLC: R_f = 0.66 (EtOAc:hexane, 70:30). ^{1}H NMR ($CDCl_3$, 200 MHz) (*trans*-isomer 2*S**,4*S**-**11b**, 26%) δ 5.76 (d, 1H, ^4J = 1.5 Hz), 4.66 (d, 1H, ^3J = 4.2 Hz), 3.81 (d, 1H, ^2J = 11.1 Hz), 3.48 (dd, 1H, ^2J = 11.1 Hz, ^4J = 1.5 Hz), 2.141 (s, 3H), 1.79 (d sept, 1H, ^3J = 4.2, ^3J = 6.9 Hz), 1.24 (s, 3H), 0.93 (d, 3H, ^3J = 6.9 Hz), 0.92 (d, 3H, 2.9 Hz), 0.77 (s, 3H). (*cis*-Isomer 2*S**,4*R**-**11b**, 74%) δ 5.57 (s, 1H), 4.41 (d, 1H, ^3J = 4.8 Hz), 3.63 (d, 1H, ^2J = 11.4 Hz), 3.44 (dd, 1H, ^2J = 11.4 Hz, ^4J = 0.6 Hz), 2.135 (s, 3H), 1.88 (d sept, 1H, ^3J = 4.8, ^3J = 6.9 Hz), 1.13 (s, 3H), 0.96 (d, 3H, ^3J = 6.9 Hz), 0.95 (d, 3H, ^3J = 6.9 Hz), 0.77 (s, 3H).

Lithium Monoalcoholate of 2,2-Dimethyl-1,3-propanediol.[14a] 2,2-Dimethyl-1,3-propanediol **13** (0.312 g, 3.0 mmol) was dissolved in 28.5 mL of dry THF under argon. The solution was cooled to 0 °C, and *n*-BuLi (1.41 mL, 3.0 mmol, 2.13 M) was added dropwise to give a 0.1 M solution of the catalyst. The colourless solution was allowed to warm to room temperature over 1 h and then cooled back to 0 °C before use.

(2,2-Dimethyl-3-hydroxylpropyl)-2-methylpropionate (9b). Dioxanol **8b** were prepared as described above. The catalyst solution described above (30 mL, 0.1 M, 30 mol %) was added at 0 °C, and after 45 min the reaction was quenched with 1.5 mL of 2 M HCl. The solvents were evaporated, and the oily residue was dissolved in 15 mL of CH_2Cl_2 and washed with 1.5 mL of water. The water phase was saturated with NaCl and washed twice with 5 mL of CH_2Cl_2. Organic phases were combined, dried over Na_2SO_4, filtered, evaporated, and purified by column chromatography (EtOAc:hexane, 40:60). Compound **9b** was obtained as a colourless oil (0.753 g, 86%). TLC: R_f = 0.55 (EtOAc:hexane, 70:30). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.93 (s, 2H), 3.29 (s, 2H), 2.63 (broad s, 1H, OH), 2.59 (sept, 1H, ^3J = 7.0 Hz), 1.22 (d, 6H, ^3J = 7.0 Hz), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) 177.8, 69.1, 68.1, 36.5, 34.1, 21.4, 19.0. EI-MS: 174 (M), 199, 101, 73, 56, 41.

5,5-Dimethyl-4-hydroxyl-2-propyl-1,3-dioxane (8a). Dimeric HPA **10** (0.204 g, 1.0 mmol) was dissolved in propanal **7a** (0.75 mL, 10 mmol, 1000 mol equiv) under argon. The solution was refluxed for 3 h, cooled to 0 °C, followed with additional stirring for 3 h. The product mixture was not acetylated but was analyzed with ^{1}H NMR. TLC: R_f = 0.60 (EtOAc:hexane, 7:3). ^{1}H NMR ($CDCl_3$, 200 MHz) (*trans*-isomer 2*S**,4*S**-**8a**; 28%) δ 5.05 (t, 1H, OCH(*n*-Pr)O, ^3J = 5.1 Hz), 4.82 (s, 1H, −OCHOH), 3.86 (d, 1H, OCH_2C, ^2J = 11.1 Hz), 3.40 (dd, 1H, OCH_2C, ^2J = 10.8 Hz, ^4J = 1.3 Hz), 1.70 (qd, 1H, ^3J = 7.5 Hz, ^3J = 5.0 Hz), 1.19 (s, 3H, ring CH_3), 0.94 (t, 3H, ^3J = 7.5 Hz), 0.83 (s, 3H, ring CH_3). (*cis*-isomer 2*S**,4*R**-**8a**, 72%) δ 4.81 (s, 1H, OCHOH), 4.55 (t, 1H, OCH(*n*-Pr)O, J = 5.1 Hz), 3.60 (d, 1H, OCH_2C, ^2J = 11.5 Hz), 3.37 (d, 1H, OCH_2C, ^2J = 11.5 Hz), 1.61 (qd, 1H, ^3J = 7.5 Hz and ^3J = 5.0 Hz), 1.08 (s, 3H), 0.97 (t, 3H, CH_3, ^3J = 7.5 Hz), 0.84 (s, 3H, ring CH_3).

(2,2-Dimethyl-3-hydroxylpropyl)-propionate (9a). Dioxanol **8a** was prepared as above. Excess propanal was evaporated at 0 °C from the product mixture. (30 min at 0.5 mmHg), yielding an oily product. The catalyst solution (30 mol %) of monolithium alcoholate of 2,2,dimethyl-1,3-propandiol (0.1 M in THF) was added in one portion. The reaction was complete after 15 min at 0 °C and was quenched with 0.5 mL of 2 M HCl. The solvent was evaporated to give white residue which was taken up with 15 mL of CH_2Cl_2. Organic phase was washed with 3 mL of brine which was then washed with 2 × 5 mL of CH_2Cl_2. All organic phases were combined, dried over Na_2SO_4, filtered, and evaporated to give 0.423 g of yellowish, oily product mixture. Column chromatography purification (CH_2Cl_2:MTBE, 9:1)

(17) Some 2,2-dimethyl-1,3-propanediol **14** is formed during the reaction. This can be removed by dissolving the product in ether and washing with small amount of water.

gave 0.131 (41% yield) of monoester **9a**. TLC: $R_f = 0.55$ (EtOAc:hexane, 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 2H), 3.30 (s, 2H), 2.37 (q, 2H, $^3J = 7.6$ Hz), 1.16 (t, 3H, $^3J = 7.0$ Hz), 0.92 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 69.2, 68.2, 36.4, 27.6, 21.4, 18.6.

5,5-Dimethyl-4-hydroxyl-2-*t*-butyl-1,3-dioxane (8c). Dimer **10** (0.205 g, 1.0 mmol) was dissolved in pivalaldehyde **7c** (1.08 mL, 10 mmol, 1000 mol equiv) under argon. The solution was stirred for 3 h at +65 °C (±3 °C) and then 3 h at 0 °C. At the end a precipitation of pivalaldehyde was obtained. TLC: $R_f = 0.64$ (EtOAc:hexane, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) (*trans*-isomer 2*S**,4*S**-**8c**, 35%) δ 4.81 (d, 1H, −OCHOH, $^4J = 0.7$ Hz), 4.82 (s, 1H, OCH(*t*-Bu)O), 3.85 (d, 1H, OCH_2C, $^2J = 10.8$ Hz), 3.39 (dd, 1H, OCH_2C, $^2J = 10.8$ Hz, $^4J = 1.1$ Hz), 1.16 (s, 3H, ring CH_3), 0.91 (s, 9H, CH_3 of *t*-Bu), 0.82 (s, 3H, ring CH_3). (*cis*-Isomer 2*S**,4*R**-**8c**, 65%) δ 4.58 (s, 1H, OCHOH), 4.19 (s, 1H, OCH(*t*-Bu)O), 3.59 (d, 1H, OCH_2C, $^2J = 11.2$ Hz), 3.33 (d, 1H, OCH_2C, $^2J = 11.2$ Hz), 1.04 (s, 1H, ring CH_3), 0.94 (s, 9H, CH_3 of *t*-Bu), 0.82 (s, 3H, ring CH_3).

(2,2-Dimethyl-3-hydroxylpropyl)-2,2-dimethylpropionate (9c). The product mixture prepared above containing mainly **8c** was heated to +10 °C because of precipitation of pivalaldehyde and the excess aldehyde was removed under reduced pressure (60 min at 0.5 mmHg). The catalyst solution of monolithium alcoholate of diol **13** (30 mol %, 0.1 M in THF) was added at 0 °C, and the reaction was stirred for 60 min at 0 °C. The reaction was quenched with 0.5 mL of 2 M HCl, and the workup was carried out as in the preparation of **9a**. Column chromatography purification (CH_2Cl_2:MTBE, 90:10) gave 0.223 g (60% yield). TLC: $R_f = 0.58$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (s, 2H), 3.28 (d, 2H, $^3J = 6.6$ Hz), 2.31 (t, 1H, $^3J = 6.6$ Hz), 1.22 (s, 9H), 0.93 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.3, 69.2, 68.2, 39.0, 36.7, 27.2, 21.3.

Dioxanols **8d**, **8f**, and **8g** from high-boiling aldehydes **7** decomposed during evaporation of excess of **7** and thus their esterification was not possible in this work. The Tishchenko reaction of **8g** was studied without the evaporation of excess aldehyde, but a large number of side products were obtained due to aldol−Tishchenko reaction, and we were not able to isolate monoester **9g**.

5,5-Dimethyl-4-hydroxyl-2-cyclohexyl-1,3-dioxane (8g). Dimer **10** (1.030 g, 5.0 mmol) was dissolved in cyclohexylcarboxaldehyde **7g** (6.1 mL, 50 mmol, 1000 mol equiv) under argon. The solution was stirred for 3 h at +65 °C and then cooled to 0 °C and stirred for another 3 h. TLC: $R_f = 0.65$ (EtOAc:hexane, 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) (*trans*-isomer 2*S**,4*S**-**8g**, 34%) δ 4.82 (d, 1H, OCH(C_6H_{11})O, $^3J = 5.0$ Hz), 4.79 (s, 1H, −OCHOH), 3.84 (d, 1H, OCH_2C, $^2J = 10.8$ Hz), 3.37 (dd, 1H, OCH_2C, $^2J = 10.8$ Hz, $^4J = 1.2$ Hz), 2.28−2.16 (m, 1H), 1.94−1.58 (m, 5H), 1.42−1.06 (m, 5H), 1.16 (s, 3H, ring CH_3), 0.81 (s, 3H, ring CH_3). (*cis*-Isomer 2*S**,4*R**-**8g**, 66%) δ 4.56 (broad s, 1H, OCHOH), 4.33 (d, 1H, OCH(C_6H_{11})O, $^3J = 5.0$ Hz), 3.58 (d, 1H, OCH_2C, $^2J = 11.3$ Hz), 3.33 (d, 1H, OCH_2C, $^2J = 11.3$ Hz), 2.28−2.16 (m, 1H), 1.94−1.58 (m, 5H), 1.42−1.06 (m, 5H), 1.04 (s, 3H), 0.81 (s, 3H, ring CH_3).

5,5-Dimethyl-4-hydroxyl-2-phenyl-1,3-dioxane (8f). Dimer **10** (1.022 g, 5.0 mmol) was dissolved in benzaldehyde **7f** (5.08 mL, 50 mmol, 1000 mol equiv) under argon. The solution was stirred for 3 h at +65 °C and then cooled to 0 °C and stirred for another 3 h. TLC: $R_f = 0.58$ (EtOAc:hexane, 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) (*trans*-isomer 2*S**,4*S**-**8f**; 42%) δ 7.92−7.86 (m, 2H), 7.68−7.46 (m, 3H), 6.08 (s, 1H, −OCH(Ph)O), 4.98 (s, 1H, −OCHOH), 4.12 (d, 1H, OCH_2C, $^2J = 11.2$ Hz), 3.42 (dd, 1H, OCH_2C, $^2J = 11.1$ Hz, $^4J = 1.2$ Hz), 1.22 (s, 3H, ring CH_3), 0.91 (s, 3H, ring CH_3). (*cis*-Isomer 2*S**,4*R**-**8f**, 58%) δ 7.92−7.86 (m, 2H), 7.68−7.46 (m, 3H), 5.58 (s, 1H, OCH(Ph)O), 4.85 (s, 1H, OCH(Ph)O), 3.58 (d, 1H, OCH_2C, $^2J = 11.3$ Hz), 3.33 (d, 1H, OCH_2C, $^2J = 11.3$ Hz), 1.15 (s, 3H, ring CH_3), 0.92 (s, 3H, ring CH_3). The compound decomposed on CI-MS analysis.

Unstable **8c** and **8d** were acetylated successfully:

4-Acetoxy-5,5-dimethyl-2-*t*-butyl-1,3-dioxane (11c). Dimer **10** (0.511 g, 2.5 mmol) and pivalaldehyde (2.75 mL, 25 mmol, 1000 mol %) were placed in a 25-mL two-necked flask under argon and stirred for 3 h at 65 °C. The solution was cooled to 0 °C and stirred for another 3 h. Pyridine (8.0 mL, 99 mmol, 4000 mol %) and acetic anhydride (9.5 mL, 101 mmol, 4000 mol %) were added at 0 °C, and the mixture was stirred overnight, allowing the temperature to rise to room temperature. Excess pyridine was removed by evaporation with toluene (3 × 20 mL). The salts were removed with filtration through a silica column. Solvents were evaporated and the products purified by column chromatography (EtOAc:hexane, 5:95). TLC: $R_f = 0.64$ (EtOAc:hexane, 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) (*trans*-isomer 2*S**,4*S**-**11c**, 35%) δ 4.81 (d, 1H, $^4J = 0.7$ Hz), 4.68 (s, 1H), 3.85 (d, 1H, $^2J = 10.8$ Hz), 3.39 (dd, 1H, $^2J = 10.8$ Hz, $^4J = 1.1$ Hz), 1.16 (s, 3H), 0.91 (s, 6H), 0.82 (s, 3H). (*cis*-Isomer 2*S**,4*R**-**11c**, 65%) δ 4.58 (s, 1H), 4.19 (s, 1H), 3.59 (d, 1H, $^2J = 11.2$ Hz), 3.33 (d, 1H, $^2J = 11.2$ Hz), 1.04 (s, 3H), 0.94 (s, 6H), 0.82 (s, 3H). IR (KBr-disk) 2974.5, 2875.0, 2854.8, 1756.4, 1466.2, 1397.5, 1373.8, 1363.9, 1230.6, 1122.6, 1008.3, 922. Analysis: Calculated for $C_{12}H_{22}O_4$ C 62.58, H 9.63; Found C 62.73, H 9.57.

4-Acetoxy-5,5-dimethyl-2-(1′-ethylpentyl)-1,3-dioxane (11d). Dimer **10** (2.046 g, 10 mmol) was dissolved in 2-ethylhexanal (9.17 mL, 101 mmol, 1000 mol-%) under argon. The colourless clear solution was heated for 3 h at +63 °C. Hexane (2 mL) was added and the solution cooled immediately to 0 °C. The solution was stirred for 3 h at 0 °C. The ratio of **10** to **8d** was 14:86. Only two diastereomers of HPA-2-ethylhexanal dimer were observed (ratio 69:31). ^{1}H NMR ($CDCl_3$, 200 MHz) (Diastereomer 1, 31%) δ 5.07 (d, 1H, OCHRO, $^3J = 2.7$ Hz), 4.81 (d, 1H, OCHOH, $^4J = 1.6$ Hz), 3.86 (d, 1H, OCH_2C, $^2J = 10.6$ Hz), 3.40 (dd, 1H, OCH_2C, $^2J = 10.6$ Hz, $^4J = 0.5$ Hz), 1.80−1.40 (m, 1H, *n*-Bu-CH-Et), 1.40−1.10 (m, 4H, 2× CH_2, CH_2CHCH_2), 1.1−0.8 (m, 12H, 4× CH_3). (Diastereomer 2, 69%) δ 4.59 (s, 1H, OCHOH), 4.56 (d, 1H, OCHRO, $^3J = 2.3$ Hz), 3.61 (d, 1H, OCH_2C, $^2J = 12.0$ Hz), 3.34 (dd, 1H, OCH_2C, $^2J = 11.4$ Hz, $^4J = 0.6$ Hz), 1.80−1.40 (m, 1H, *n*-Bu-CH-Et), 1.40−1.10 (m, 4H, 2× CH_2, CH_2CHCH_2), 1.1−0.8 (m, 12H,

4× CH_3). Acetylation was carried out as with **8b** and column chromatographic purification (EtOAc:hexane) gave a diastereomeric mixture of **11d** in 34% isolated yield (1.86 g). TLC: $R_f = 0.40$ (EtOAc:hexane, 20:80). ^{1}H NMR ($CDCl_3$, 400 MHz) (*cis*-isomer 2*S**,4*R**-**11d**, 65%) δ 5.56 (d, 1H, ^2J = 0.9 Hz), 4.60 (dd, 1H, ^3J = 5.9 Hz, ^3J = 2.2 Hz), 3.63 (d, 1H, ^2J = 11.4 Hz), 3.43 (d, 1H, ^2J = 11.4 Hz), 2.14 (s, 3H), 1.60−1.25 (m, 9H), 1.13 (s, 3H), 0.76 (s, 3H), 0.95−0.85 (m, 6H), 0.76 (s, 3H). (*trans*-Isomer 2*S**,4*S**-**11d**, 35%) δ 5.77 (d, 1H, ^3J = 1.5 Hz), 4.87 (dd, 1H, ^3J = 3.3 Hz, ^3J = 1.1 Hz), 3.80 (d, 1H, ^2J = 10.8 Hz), 3.49 (dd, 1H, ^2J = 11.1 Hz, ^4J = 1.7 Hz), 2.12 (s, 3H), 1.60−1.25 (m, 9H), 1.24 (s, 3H), 0.93−0.85 (m, 6H), 0.76 (s, 3H).

X-ray crystal data of 11c:[18] formula $C_{12}H_{22}O_4$, M = 230.30, colorless crystal 0.58 mm × 0.13 mm × 0.13 mm, a = 6.077(1) Å, b = 9.311(1) Å, c = 12.580(1) Å, α = 72.34(1)°, β = 89.02(1)°, γ = 75.20(1)°, V = 654.36(14) Å^3, ρ_{calc} = 1.169 g cm^{-3}, μ = 0.086 mm^{-1}, no absorption correction, Z = 2, triclinic, space group *P*-1 (No. 2), λ = 0.71073 Å, T = 173 K, ω and φ scans, 4970 reflections collected, [(sin θ)/λ] = 0.65 Å^{-1}, 2971 independent (R_{int} = 0.024) and 2170 observed reflections [$I \geq 2\sigma(I)$], 146 refined parameters, R = 0.047, wR2 = 0.104, largest diff. peak and hole 0.21 (−0.23) e Å^{-3}, hydrogens calculated and refined as riding atoms.

(18) Crystallographic data (excluding structure factors) for **8c** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 162042. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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