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STEREOCONTROLLED SYNTHESIS OF (*R*R**)- AND (*R*S**)-5-HYDROXY-2-METHYLHEXANOIC ACID LACTONES

PHEROMONE OF THE CARPENTER BEE VIA PALLADIUM-CATALYZED REACTIONS

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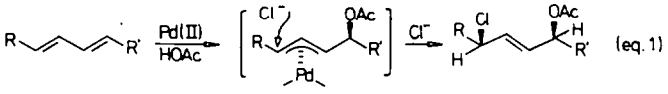
Abstract—(*E, Z*)-2,4-Hexadiene was transformed to the lactone *cis*-**1** (>93% *cis*) (pheromone of the carpenter bee) in a stereospecific reaction sequence *via* a Pd-catalyzed 1,4-acetoxychlorination. The same reaction sequence applied to (*E, E*)-2,4-hexadiene afforded the isomeric lactone *trans*-**1** (>91% *trans*).

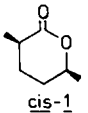
The control of the relative stereochemistry at chiral carbons in acyclic systems is a challenging problem in organic synthesis.[1] Diastereoselective control in the generation of chiral centra with a 1,2-relationship, i.e. *erythro*- and *threo*-selectivity, can be successfully obtained by a number of general methods.[1,2] However, the control of the relative stereochemistry between distant carbons is more difficult and general methods for achieving such a diastereoselectivity are rare. Because of the great number of natural products having a defined relative stereochemistry between distant carbon centra, methods for obtaining stereocontrol between remote centra are highly desirable.

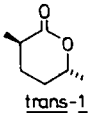
We have recently developed stereoselective Pd-catalyzed 1,4-additions to conjugated dienes, that allow the control of the 1,4-relative stereochemistry at carbons in an acyclic system.[3-5] In one of these reactions a chloro group and an acetoxy group are stereospecifically added across the diene to the 1,4-positions (Eq. 1).[3,4] The stereocontrol of the reaction depends on the stereospecific *trans*-addition to one of the double bonds to yield one diastereoisomer of the π-allyl-palladium intermediate. External *trans*-attack by chloride ion on the π-allyl group affords the chloroacetate.



Other methods for obtaining a similar control of 1,4-relative stereochemistry at carbon include transition-metal catalyzed nucleophilic addition to 1,3-diene monoepoxides.[6-8] The stereoselectivity of these reactions has mainly been studied in cyclic systems, although control of the 1,4-relative stereochemistry was recently demonstrated for the palladium-catalyzed alkylation of an acyclic 1,3-diene monoepoxide.[8]

An important aspect of the acetoxychlorination reaction shown in Eq. (1) is that the chloro and acetoxy groups can be sequentially substituted (Scheme 1). This principle was applied to a pheromone synthesis using the chloroacetate from isoprene.[9] An advantage with the acetoxychlorination approach over the metal-catalyzed nucleophilic addition to 1,3-diene monoepoxide is that there is a choice of stereochemistry in the nucleophilic substitution of the chloro group. The chloro group can be displaced either with retention using metal catalysis or with inversion in an ordinary S_N2-reaction. This dual stereoselectivity was demonstrated in both cyclic and acyclic systems.[4] In this paper we demonstrate the synthetic utility of the palladium-catalyzed 1,4-acetoxychlorination reaction by transforming (*E, Z*)- and (*E, E*)-2,4-hexadiene in a stereospecific manner to the (*R*S**)- and (*R*R**)-isomers (*cis*-**1** and *trans*-**1**) respectively of 5-hydroxy-2-methylhexanoic acid lactone. The (*R*S**)-isomer (*cis*-**1**)


cis-1

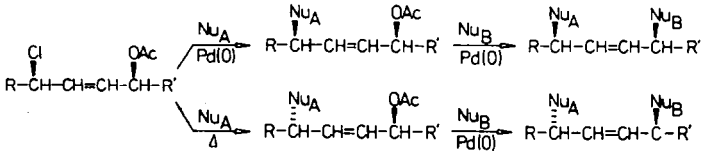

trans-1

is the major component of the carpenter bee pheromone.[10]

RESULTS AND DISCUSSION

The lactone *cis*-**1** was isolated in 1976 by Wheeler *et al.*[10] and was found to be the key component of the sex attractant of the carpenter bee (*Xylocopa hirutissima*). Since then several syntheses of the lactones *cis*-**1** and *trans*-**1** have been reported including preparation of enantiomerically pure material.[10-13] None of the previous methods allow the stereoselective synthesis of both isomers *cis*-**1** and *trans*-**1**, but give either only one of the isomers or a mixture of both isomers that must be separated. In the sequence shown in Scheme 2, (*E, Z*)- and (*E, E*)-2,4-hexadiene are transformed in a stereospecific synthesis to the lactones *cis*-**1** and *trans*-**1** respectively via a palladium-catalyzed 1,4-acetoxychlorination.

Pd-catalyzed acetoxychlorination of (*E, Z*)-2,4-hexadiene in acetic acid at room temperature proceeds with high regio- and stereoselectivity to produce only one diastereoisomer, (*R*S**)-**2** (>95% *R*S**). The diastereomeric purity of **2** was established by ^{1}H-NMR

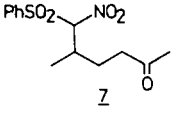


Scheme 1.

spectroscopy. The approach to lactones *cis*-1 and *trans*-1 requires the displacement of the chloro group by a carboxy anion equivalent and subsequent reduction of the double bond. Attempts to replace the chloro group by cyanide (NaCN–DMSO, KCN–18-crown-6, or $Bu_4N^+CN^-$) failed and resulted in elimination of the acetoxy group. Several other ways of stereospecifically introducing a —COOH group, such as metal-catalyzed carbonylation of lithiumdithiane, were also tried without success.

It was recently reported that (phenylsulfonyl)nitromethyl anion can be used as a carboxy anion equivalent.[14] We found that this method worked excellently in our system for introducing a masked —COOH group. Pd-catalyzed substitution of the chloro group in the chloroacetate (*R*S**)-2 with (phenylsulfonyl)nitromethyllithium takes place under mild conditions (7 hr, 25°) with complete (>99%) retention of configuration at carbon. Subsequent hydrolytic workup afforded the alcohol (*R*S**)-3 in an isolated yield of 81%.

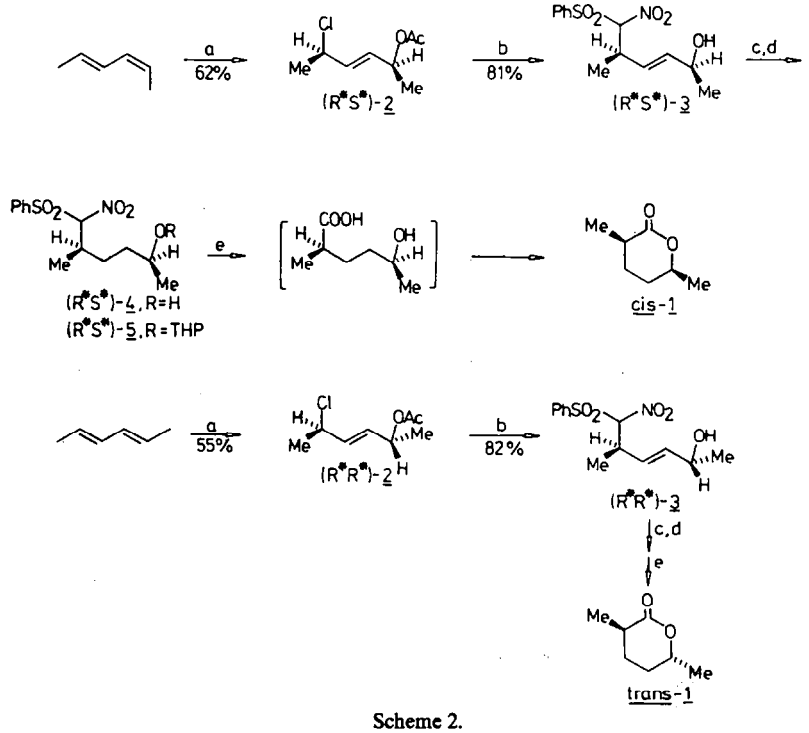
For the hydrogenation of the double bond in (*R*S**)-3 we first tried PtO_2/H_2, since the related *meso*-3-hexen-2,5-diol is hydrogenated in less than 1 hr at room temperature by this system, without allylic C—O cleavage and with retention of *meso* stereochemistry.[5b] Surprisingly, hydrogenation of (*R*S**)-3 using PtO_2/H_2 was extremely slow and not synthetically useful, since prolonged reaction time resulted in several other products. We therefore tried other hydrogenation catalysts. Wilkinson's catalyst $RhCl(PPh_3)_3$[15] gave (*R*S**)-4 with complete retention of the *R*S** stereochemistry in an acceptable yield with some competing rearrangement to the ketone 7. It is



7

fortunate that 7 stays at the ketone stage without being reduced under the reaction conditions, since this would have resulted in a severe destruction of the stereospecificity in the reaction sequence outlined in Scheme 2.

The transformation of the (phenylsulfonyl)-nitromethyl group to a —COOH group utilizes potassium permanganate in an alkaline aqueous medium.[14] It was therefore necessary to protect the alcohol group via the O-tetrahydropyranyl derivative (*R*S**)-5. Oxidation of the tetrahydropyranyl derivative (*R*S**)-5 using the procedure described by Wade *et al.*,[14] followed by acidic workup gave (*R*S**)-5-hydroxy-2-hexanoic acid ((*R*S**)-6), which spon-



Scheme 2.

taneously ring-closed to the lactone *cis*-**1** (>93% *cis*). The lactone *cis*-**1** was characterized by its ^{1}H-NMR and IR spectra, which were identical to those reported for *cis*-**1**.[10,11b]

The same reaction sequence was applied to (*E*,*E*)-2,4-hexadiene, which was converted to the isomeric lactone *trans*-**1** (>91% *trans*). The slightly lower stereospecificity in this case depends partly on the Pd-catalyzed 1,4-acetoxychlorination step, which affords a 94:6 mixture of chloroacetates (*R**R**)-**2** and (*R**S**)-**2**. It is interesting to note the high stereospecificity in the Pd-catalyzed alkylation reactions of the chloroacetates **2** to give **3**, which in both cases occurs with >99% retention of configuration at carbon. The retention stereochemistry is in accord with a Pd-catalyzed reaction through a π-allyl-Pd intermediate.[16] As observed previously, Pd-catalyzed substitution of allylic chlorides is more stereospecific than substitution of the corresponding allylic acetates.[4a] This is most likely because the allylic acetates can undergo Pd-catalyzed isomerization prior to reaction,[17] which appears not to be the case with allylic chlorides.

It was not possible to displace the chloride in chloroacetate **2** with (phenylsulfonyl)nitromethyl anion in an ordinary S_N2 reaction. Thus, treatment of (*R**S**)-**2** with (phenylsulfonyl)nitromethyllithium in acetonitrile at 80° for 20 hr, followed by GLC analysis, showed that the chloroacetate was completely unreacted.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 421 spectrometer. The NMR spectra were obtained with a Bruker WP 200 MHz FT spectrometer. Mass spectra were measured with an LKB 9000 spectrometer. GLC analyses were performed on a column of 5% SE-30 on Chromosorb W. High pressure liquid chromatography (HPLC) was performed on a Waters M-45 instrument with a microporasil column (silica, 10 μm packing, 0.4 × 30 cm).

(*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene were purchased from FLUKA AG and used without purification. $Pd(PPh_3)_4$ was prepared according to Coulson[18] or more conveniently by treatment of $Pd(PhCN)_2Cl_2$[19] in acetone at 0° in order with butadiene, diethylamine and finally PPh_3.[4a] $Rh(PPh_3)_3Cl$ was prepared according to Osborn *et al.*[15a] Tetrahydrofuran (THF) was distilled over potassium/benzophenone under N_2.

(*R**S**)-2-*Acetoxy*-5-*chloro*-3-*hexene* ((*R**S**)-**2**). To a slowly stirred soln of $Pd(OAc)_2$ (504 mg, 2.25 mmol), LiCl (2.52 g, 60 mmol), $LiOAc \times 2H_2O$ (6.12 g, 60 mmol), and *p*-benzoquinone (6.6 g, 60 mmol) in AcOH (100 ml) at 25° was added (*E*,*Z*)-2,4-hexadiene (2.46 g, 30 mmol) in pentane (150 ml). The mixture was stirred for 24 hr at 25°. Sat NaCl aq (60 ml) was added and the mixture was stirred for 5 min and then filtered. The pentane phase was collected and the aqueous phase was extracted with pentane–ether (90:10) (3 × 200 ml). The combined organic phase was washed with water (2 × 100 ml), sat Na_2CO_3 aq (50 ml), 2 M NaOH (50 ml), water (50 ml) and sat NaCl aq (50 ml) and dried ($MgSO_4$). Most of the solvent was distilled off at atmospheric pressure and the final amount of solvent was removed on a rotary evaporator under reduced pressure (water aspirator) to afford 3.36 g (64%) of essentially pure product. Kugelrohr distillation (55–70°, 0.1 Torr) afforded 3.27 g (62%) of (*R**S**)-**2** (>95% *R**S**). The compound is fully characterized in the paper of ref. 4*b*, but for completeness we give the NMR spectrum: ^{1}H-NMR ($CDCl_3$) δ 5.82, 5.72 (AB part of ABMY system, 2H, CH=CH), 5.36 (m, 1, CH—OAc), 4.53 (m, 1H, CH—Cl), 2.06 (s, 3H, OAc), 1.60 (d, 3H, CH_3), 1.32 (d, 3H, CH_3). For the detection of the *R**R** isomer see below.

(*R**R**)-2-*Acetoxy*-5-*chloro*-3-*hexene* ((*R**R**)-**2**) was prepared by the same method from (*E*,*E*)-2,4-hexadiene (2.46 g, 30 mmol) but the diene was added in four portions (at 0, 6, 12, 18 hr of reaction time). Workup as above afforded after Kugelrohr distillation 2.9 g (55%) of (*R**R**)-**2** (*R**R** : *R**S** = 94:6) contaminated with small amounts of Diels–Alder adduct (between benzoquinone and diene). (*R**R**)-**2** is fully characterized in ref. 4*b*. The ^{1}H-NMR spectrum (200 MHz) is very similar to the one of (*R**S**)-**2** but differs slightly in the olefinic region.[4b] The high field olefinic proton of (*R**R**)-**2** appears at ≈2 Hz lower field than the corresponding proton in (*R**S**)-**2**.

(2*R**5*S**)-5-((*Phenylsulfonyl*)*nitromethyl*)-3-*hexen*-2-*ol* ((*R**S**)-**3**). To a soln of (phenylsulfonyl)nitromethyllithium[14] (7.10 g, 34.1 mmol) and $Pd(PPh_3)_4$ (490 mg, 0.425 mmol) in freshly distilled THF (50 ml) under N_2 at room temp was added (*R**S**)-**2** (1.5 g, 8.5 mmol) dissolved in THF (20 ml) and dodecane (50 μl), as internal standard. The mixture was stirred at room temp and followed by GLC. When all (*R**S**)-**2** had been consumed (7.5 hr) the solvent was evaporated and MeOH (100 ml) was added together with 2 M NaOH (15 ml). The mixture was refluxed for 20 min and then allowed to cool to ambient temp. The MeOH was removed *in vacuo* and to the remaining mixture (≈10–15 ml) was added CH_2Cl_2 (40 ml). The mixture was acidified (pH ≈1) with 4 M HCl and the organic phase was collected. The aqueous phase was further extracted with CH_2Cl_2 (3 × 25 ml) and the organic phases were combined, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (230–400 mesh, eluation with EtOAc/hexane 50:50, containing 100 μl HCl/l) to afford 2.06 g (81%) of (*R**S**)-**3**; Because of the chiral carbon of the (phenylsulfonyl)nitromethyl group there are two 2*R**,5*S** diastereoisomers in approximately equal amounts. IR (neat) 3540, 3380, 2960, 1555, 1445, 1330, 1150, 1080, 760, 720, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (pair of diastereoisomers) δ 7.95–7.56 (m, 5H, aromatics), 5.82–5.47 (m, 2H, CH=CH), 5.40, 5.36 (two d (overlapping), J = 8.8 and 9.6 Hz, 1H, CH—NO_2), 4.35, 4.20 (m, 1H, CH—O), 3.21 (m, 1H, CH), 1.62 (br s, 1H, OH), 1.43, 1.31 (d, J = 6.7 and 6.4 Hz, 3H, CH_3), 1.18, 1.17 (d, J = 6.4 and 6.7 hHz, 3H, CH_3). (Found: C, 52.01; H, 5.79. Calc for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72.)

(2*R**5*R**)-5-((*Phenylsulfonyl*)*nitromethyl*)-3-*hexen*-2-*ol* ((*R**R**)-**3**). The same procedure as for the preparation of (*R**S**)-**3** was used. (*R**R**)-**2** (1.72 g, 6.1 mmol) afforded 2.40 g (82%) of (*R**R**)-**3**: IR (neat) 3520 (br), 3380 (br), 2960, 1560, 1445, 1335, 1145, 1080, 970, 910, 785, 760; ^{1}H-NMR ($CDCl_3$) (pair of diastereoisomers ≈ 1:1) δ 8.0–7.5 (m, 5H, aromatics), 5.83–5.47 (m, 2H, CH=CH), 5.41, 5.36 (two d, J = 6.6 and 6.7 Hz, 1H, CH—NO_2), 4.33, 4.21 (m, 1H, CH—O), 3.22 (m, 1H, CH), 1.73 (br s, 1H, OH), 1.43, 1.29 (two d, J = 6.8 and 6.4 Hz, 3H, CH_3), 1.18, 1.16 (two d, J = 6.4 and 6.8 Hz, 3H, CH_3). (Found: C, 52.02; H, 5.73. Calc for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72%.)

(2*R**5*S**)-5-((*Phenylsulfonyl*)*nitromethyl*)-*hexan*-2-*ol* (*R**S**-**4**). (*R**S**)-**3** (1.5 g, 5 mmol) and $Rh(PPh_3)_3Cl$ (193 mg, 0.2 mmol) were stirred in abs EtOH (40 ml) in a glass autoclave under a H_2 pressure (gauche pressure = 6.5 kg/cm^2) at 50° for 42 hr. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether. After filtering and evaporation of the ether, the residue was purified by flash column chromatography on silica gel (230–400 mesh, eluation with EtOAc/hexane 50:50 containing 100 μl HCl/l) to give 794 mg (53%) of (*R**S**)-**4** and 280 mg (19%) of **7**. (*R**S**)-**4**: IR (neat) 3540, 3380, 2980, 1560, 1550, 1445, 1330, 1145, 755, 715, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (pair of diastereoisomers) δ 8.0–7.5 (m, 5H, aromatics), 5.44, 5.38 (two d, J = 7.8 and 9.1 Hz, 1H, CH—NO_2), 3.84, 3.74 (m, 1H, CH—O), 2.63 (m, 1H, CH), 1.7–1.4 (m, 5, CH_2CH_2 and OH), 1.34, 1.24 (two d, J = 6.7 and 6.2 Hz, 3H, CH_3), 1.17, 1.08 (two d, J = 6.2 and 6.7 Hz); *m/e* 301 (M^+), 286, 253, 218.

Compound **7**: IR (neat) 2980, 1710, 1555, 1450, 1330, 1150, 1080, 760, 715, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (pair of diastereomers ≈ 1:1) δ 8.0–7.5 (m, 5H, aromatics), 5.42, 5.37 (two d, J = 7.2 and 9.1 Hz, 1H, CH—NO_2), 2.85–2.40 (m, 3H, CH and CH_2CO), 2.19, 2.14 (two s, 3H, CH_3CO), 1.80 (m, 1H,

one proton in CH_2), 1.59 (m, 1H, one proton in CH_2), 1.33, 1.06 (two d, J = 6.8 and 6.8 Hz, 3H, CH_3).

(2*R**5*R**) - 5 - ((*Phenylsulfonyl*)*nitromethyl*) - *hexan* - 2 - *ol* ((*R***R**)-4). The same hydrogenation procedure as for the preparation of (*R***S**)-4 was used. (*R***R**)-3 (375 mg, 1.25 mmol) afforded 181 mg (48%) of (*R***R**)-4 and 125 mg (33%) of 7. (*R***R**)-4: IR (neat) 3560–3300 (br), 2960, 1555, 1450, 1335, 1150, 1080, 760, 720, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (pair of diastereoisomers) δ 8.0–7.5 (m, 5H, aromatics), 5.43, 5.38 (two d, J = 7.6 and 9.3 Hz, 1H, CH—NO_2), 3.83, 3.72 (m, 1H, CH—O), 2.61 (m, 1H, CH), 1.65–1.38 (m, 5H, CH_2CH_2 and OH), 1.35, 1.23 (two d, J = 6.8 and 6.2 Hz, 3H, CH_3), 1.16, 1.08 (two d, J = 61 Hz, 3H, CH_3); *m/e* 301 (M^+), 286, 253, 218.

(2*R**5*S**) - 5 - ((*Phenylsulfonyl*)*nitromethyl*) - (O - *tetrahydropyranyl*)*hexan* - 2 - *ol* ((*R***S**-5). To a stirred soln of (*R***S**)-4 (502 mg, 1.67 mmol) and dihydropyrane (280 mg, 3.34 mmol) in dry CH_2Cl_2 (8.5 ml) was added *p*-toluenesulfonic acid (6 mg). The mixture was stirred at room temp for 20 min, and then filtered through a short column of silica. The column was eluted with EtOAc/hexane (30:70). Evaporation of the solvent afforded 554 mg (86%) of (*R***S**)-5: IR (neat) 2930, 1555, 1450, 1335, 1150, 1075, 1020, 990, 760, 720, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (mixture of four diastereoisomers) δ 8.0–7.5 (m, 5H, aromatics), 5.50–5.35 (m (four overlapping doublets), 1H, CH—NO_2), 4.7–4.5 (m, 1H, O—CH—O), 4.0–3.58 (m, 2H, CH—O and one proton in CH_2—O), 3.57–3.35 (m, 1H, one proton in CH_2—O), 2.7–2.48 (m, 1H, CH), 2.0–1.4 (m, 10, five CH_2 groups), 1.37–1.04 (m (eight overlapping doublets), 6H, CH_3 groups).

(2*R**5*R**) - 5 - (*Phenylsulfonyl*)*nitromethyl* - (O - *tetrahydropyranyl*)*hexan* - 2 - *ol* (*R***R**-5). The same procedure as for the preparation of (*R***S**)-5 was used. (*R***R**)-4 (150 mg, 0.498 mmol) afforded 189 mg (99%) of (*R***R**)-5: IR (neat) 2930, 1555, 1450, 1335, 1150, 1080, 1025, 990, 760, 720, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) (mixture of four diastereoisomers) δ 8.07–7.5 (m, 5H, aromatics), 5.47–5.33 (m, 1H, $CHNO_2$), 4.7–4.5 (m, 1H, O—CH—O), 4.0–3.59 (m, 2H, CH—O and one proton in CH_2—O), 3.58–3.35 (m, 1H, one proton in CH_2—O), 2.68–2.44 (m, 1H, CH), 2.0–1.4 (m, 10, five CH_2 groups), 1.37–1.04 (m (eight overlapping doublets), 6H, CH_3 groups).

(*R***S**)-5-*Hydroxy*-2-*methylhexanoic acid lactone* (cis-1). (*R***S**)-4 (110 mg, 0.286 mmol) was dissolved in 9 ml of aqueous 1.3 M NaOH under vigorous stirring. To this soln was added a soln of $KMnO_4$ (1.18 g, 7.5 mmol) in water (50 ml) at 15–20° during 30 min under stirring. The mixture was allowed to stir for another 30 min and then $NaHSO_3$ (2.2 g) was added under cooling. The resulting ppt was removed by centrifugation. The weakly alkaline soln (pH ≈8–9) was concentrated *in vacuo* to *ca* 6 ml and acidified with 2 M HCl (pH ≈2). EtOH (3 ml) was added and the resulting soln was heated to 50° for 10 min. The soln was cooled, alkalified (pH ≈9) with sat Na_2CO_3 aq, concentrated to *ca* 6 ml and washed with ether (2 × 5 ml). The aqueous phase was acidified with 4 M HCl (pH ≈2–3) and extracted with ether (6 × 15 ml). The organic phase was dried (Na_2SO_4) and concentrated, first under atmospheric pressure (oil bath, 65°) then under reduced pressure (60 Torr, 20°) and the residue was dissolved in CH_2Cl_2 (5 ml) and dried (Na_2SO_4). Cautious evaporation of the solvent under reduced pressure and Kughelrohr distillation (60–70°, 0.1 Torr) of the residue afforded 21 mg (58%) of *cis*-1 (>93% *cis*). The spectral data are consistent with those reported.[10,11b] ^{1}H-NMR ($CDCl_3$) δ 4.47 (m, 1H, CH—O), 2.59 (m, 1H, CH), 2.2–1.4 (m, 4H, CH_2CH_2), 1.36 (d, J = 6.2 Hz, 3H, CH_3), 1.23 (d, J = 6.8 Hz, 3H, CH_3).

(*R***R**)-5-*Hydroxy*-2-*methylhexanoic acid lactone* (trans-1). The same oxidation procedure was applied to (*R***R**)-5 (145 mg, 0.377 mmol), which afforded 32 mg (66%) of *trans*-1 (>91% *trans*). The spectral data are consistent with those reported.[10,11b] ^{1}H-NMR ($CDCl_3$) δ 4.44 (m, 1H, CH—O), 2.43 (m, 1H, CH), 2.1–1.4 (m, 4H, CH_2CH_2), 1.37 (d, 6.2 Hz, 3H, CH_3), 1.30 (d, 7.0 Hz, 3H, CH_3).

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