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Enantio- and Diastereoselectivity in the Reduction of Spiro[4.5]decane-1,4-dione Derivatives with Baker's Yeast

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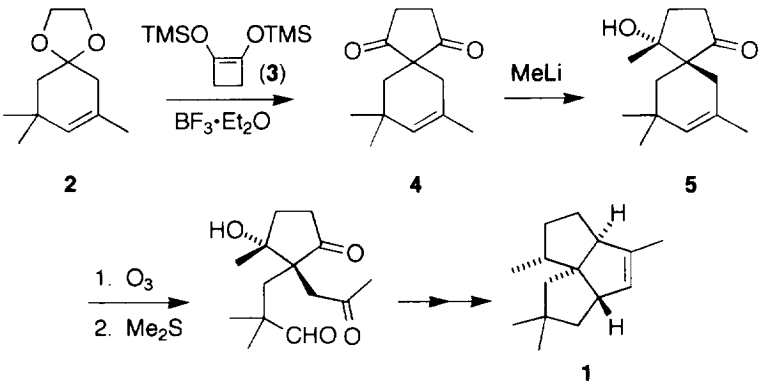
Abstract: Reductions mediated by baker's yeast were carried out on five spiro[4.5]decane-1,4-dione derivatives **4**, **9**, **12**, **15**, and **18**. Enantioselectivity was always very high, but this did not correlate with the facial diastereoselectivity, which ranged from very high to zero. In some instances, the facial selectivity of the yeast-mediated reduction was lower than that of $NaBH_4$. The reduction product of **4** was transformed in a few steps to the enatiomerically enriched form of a bicylic intermediate **5** for the synthesis of the angular triquinane pentalenene **1**. The yeast-mediated reduction of spirodiketone **21** demonstrated that reduction of the equatorial carbonyl was very much the preferred mode of reaction.

INTRODUCTION

Our spiro-annulation route[1] to the sesquiterpene pentalenene **1** relied on the Lewis acid-catalyzed geminal acylation reaction[2-5] of the acetal of a simple cyclohexenone derivative (**2**) with 1,2-bis-(trimethylsilyloxy)-cyclobutene (**3**) to afford the critical spirocyclic linkage in diketone **4**. Stereogenic centers evolved during the subsequent attack of methyllithium on **4**, and the result was the production of the keto-alcohol **5** in racemic form. This was opened by ozonolysis, and then two straightforward aldol condensations were used to cyclize to the racemic angular triquinane system in very good overall yield.

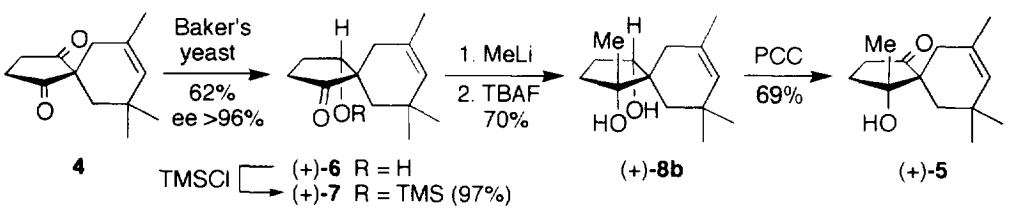


2 **4** **5** **1**

Modification of this approach to afford **1**, or any of its more highly oxygenated congeners,[6] in an enantiomerically enriched form would entail the enantioselective formation of **5**. Chiral reductions of 1,3-diketones by the action of baker's yeast (*Saccharomyces cerevisiae*) have been studied extensively.[7-9] The reduction of 1,3-cyclopentanediones doubly substituted at C-2 was shown to take place with generally very high enantioselectivity, and the new stereogenic carbinol center was invariably *S*. Also, with substrates that were plane-nonsymmetric (i.e., the two substituents at C-2 were not the same), addition of hydrogen to the sterically less hindered face of a carbonyl was favored, just as with $NaBH_4$, but the yeast-mediated reduction was significantly more diastereoselective than was $NaBH_4$.[8] The facial selectivity of additions of $NaBH_4$ and of methyllithium to spiro[4.5]decane-1,4-dione derivatives, including **4**, was examined a few years ago.[10] The selectivity, which in some instances was very high, appeared to be more consistant with stereoelectronic control rather than a steric control. This led to the interesting question of yeast-mediated reduction of these spiro-diketones, and, more specifically, whether **4** could be transformed via yeast-mediated reduction into enantiomerically homogeneous **5**.

RESULTS AND DISCUSSION

Baker's yeast reductions were carried out using a procedure based on that of Mori.[9a] The reduction of diketone **4** provided a single, optically active product **6** in 62% isolated yield, and 23% of **4** was recovered. The NMR spectra of **6** showed that it was the same diastereomer as the racemic product of reduction of **4** by $NaBH_4$. X-ray crystallography was used to establish the relative stereochemistry of the TMS-ether **7** unequivocally.[11] Only one enantiomer of yeast-derived **6** was detectable by ^1H NMR in a lanthanide-induced shift study using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) as the chiral shift reagent. Furthermore, the ^1H, ^{13}C, and ^{19}F NMR spectra of its (+)-α-methoxy-α-trifluoromethylphenylacetyl [(+)-MTPA] ester,[12] showed only one set of signals. A negative Cotton effect in the CD spectrum[13] of **6** was consistant with the absolute stereochemistry as (4*S*,5*R*).

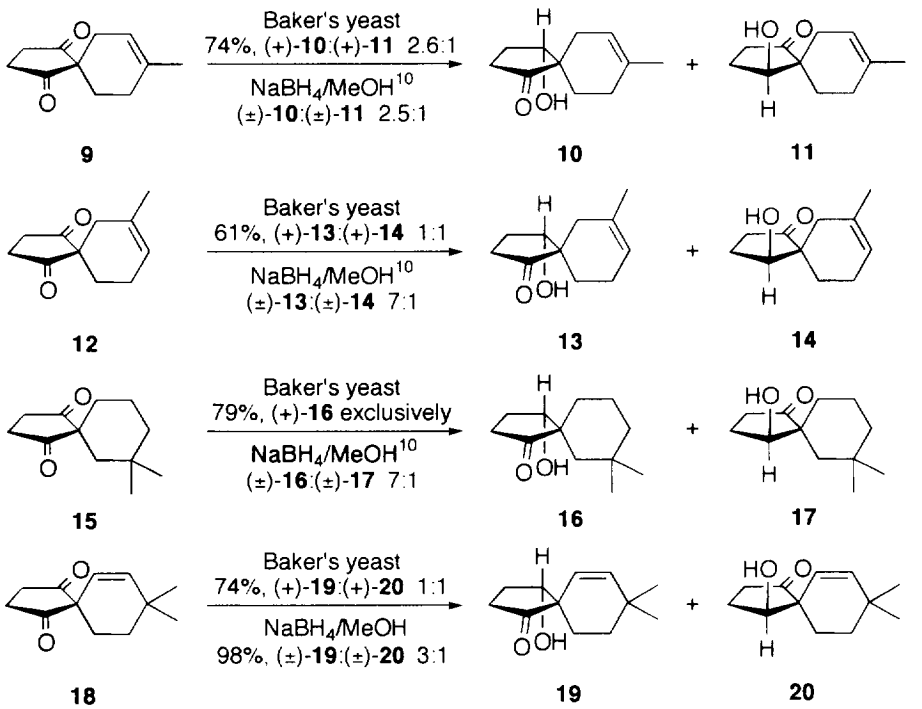


Treatment of the TMS-ether **7** with one equivalent of MeLi resulted largely in the formation of enolate, but six cycles of MeLi-then-quench afforded the tertiary alcohol, which, without purification, was desilylated to give two isomers (7:1) of diol **8**, epimeric only at C-1, in good yield. Oxidation of the major epimer **8b** gave **5**, which had the correct absolute configuration at the spirocyclic center for natural pentalenene **1**.[6]

Reduction of diketone **9** by $NaBH_4$ had resulted in much poorer facial selectivity. The racemic keto-alcohols **10** and **11** were obtained in a ratio of only 2.5:1, respectively.[10] The yeast-mediated reduction proceeded with almost the same facial selectivity (2.6:1) as the $NaBH_4$ reduction. However, this mixture of keto-alcohols was optically active, but when this mixture was transformed into (+)-MTPA esters the ^1H, ^{13}C, and

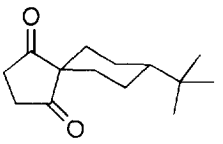
^{19}F NMR spectra still showed only two sets of signals. Therefore, the yeast-mediated reaction must have had very high enantioselectivity, in spite of the poor facial diastereoselectivity.

The $NaBH_4$ reduction of diketone **12** showed a better level of facial selectivity, with racemic **13** and **14** being produced in a 7:1 ratio.[10] Once again, yeast-mediated reduction took place with very high enantioselectivity, but there was no facial selectivity whatsoever. The vinyl methyl group of **12** was in the same position as the vinyl methyl group of **4**. Therefore, it is unlikely that this methyl in **4** played any role in determining the yeast's selectivity with **4**. On the other hand, keto-alcohol **16** was the only product detected from the yeast-mediated reduction of diketone **15**, but the $NaBH_4$ reduction of **15** had given racemic **16** and **17** in a 7:1 ratio.[10] Therefore, facial selectivity in the yeast-mediated reduction of **4** seemed to be controlled completely by its gem-dimethyls, whereas with $NaBH_4$ the facial selectivity was the result of influences from both the vinyl methyl and the gem-dimethyls. Since the yeast had shown some facial selectivity with **9**, albeit very modest, it seemed reasonable to think that the yeast-mediated reduction of diketone **18** might also show some facial selectivity. This proved to be incorrect. A 1:1 ratio of **19** to **20** was obtained. As before, the enantioselectivity was very high, and the ^1H NMR spectrum of the product of esterification of the mixture with (+)-MTPA chloride showed only two sets of ester signals, even though the two esters had identical ^{19}F NMR shifts. $NaBH_4$ reduction of **18** gave racemic **19** and **20** in a 3:1 ratio.



At any moment in time, one of the carbonyls of a spiro-diketone is pseudo-axial (or axial), and the other carbonyl is pseudo-equatorial (or equatorial) with respect to the cyclohexene (or cyclohexane) ring. We had established with the conformationally restricted diketone **21** that $NaBH_4$ reduction takes place very predomin-

antly on the equatorial carbonyl, i.e., **22** rather than **23** is is major (racemic) product.[10] In this instance, the facial selectivity with baker's yeast was very similar. Indeed, only **22** was detected, and its (+)-MTPA ester was a single diastereomer. It is not surprising that **22** was the major product because the equatorial carbonyl of **21** was obviously less encumbered than the axial carbonyl. The small, positive Cotton effect in the CD spectrum of **22** was an unreliable indicator for its absolute stereochemistry, but the X-ray crystal structure of the (+)-MTPA ester left no doubt that **22** was the 4*S* enantiomer.[11]



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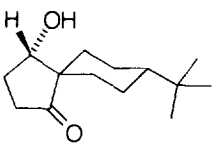

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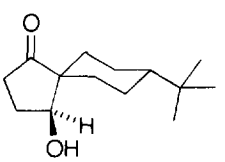

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In conclusion, this work has shown that baker's yeast-mediated reductions of spiro[4.5]decane-1,4-dione derivatives takes place with very high enantioselectivity, but the facial diastereoselectivity ranged from excellent to nonexistant. It appears that, because substrate orientation in the active site of baker's yeast is likely to be very largely dependent of steric factors,[7] yeast-mediated reductions cannot benefit significantly from stereoelectronic phenomena. In some instances this allows a simple reducing agent, such as $NaBH_4$, to react with better facial diastereoselectivity, in contrast with some simpler 2,2-disubstituted 1,3-cyclopentanediones.[8] Conversely, the fact that facial selectivity in the $NaBH_4$ reductions showed a different pattern of selectivity lends credence to the suggestion that facial selectivity in the $NaBH_4$ reductions of spirocyclic diketones such as **4** may be influenced significantly by a stereoelectronic phenomenon.[10]

EXPERIMENTAL

Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Specific rotations were determined with a Perkin Elmer 141 polarimeter. Circular dichroism (CD) measurements were made on a Jasco J40A instrument using a cell of 0.05 cm path length. Infrared (IR) spectra were recorded on a Mattson FT instrument as thin films. Nuclear magnetic resonance (NMR) spectra were obtained on a General Electric GE 300-NB instrument as $CDCl_3$ solutions. In nearly every instance, the ^{13}C NMR chemical shift is followed in parentheses by the number of attached protons, as determined by APT and/or heteronuclear correlation spectra. Nuclear Overhauser effect (NOE) measurements were made from sets of interleaved ^1H experiments (16K) of 8 transients cycled 12 to 16 times through the list of frequencies to be saturated. The decoupler was gated on continuous wave mode for 6 sec with sufficient attenuation to give a 70-90% reduction in intensity of the irradiated signal. frequency changes were preceded by a 60-sec delay. Four scans were used to equilibrate spins before data acquisition, but a relaxation delay was not applied between scans at the same frequency. NOE difference spectra were obtained from zero-filled 32K data tables to which a 1 to 2 Hz exponential line-broadening function had been applied. Mass spectral (MS) data were obtained with a V.G. Micromass 7070HS instrument, except in some instances in which data were from a Hewlett-Packard 5970 mass selective detector (GC-MS). MS data have this form: *m/z* (% of base peak). We have previously reported the preparation of

diketones **4**,[1] **6**,[3,4] **18**,[5] and **21**.[5] Diketones **9**, **12**, and **15** were prepared by the Lewis acid-catalyzed geminal acylation of the corresponding acetals with **3**.[3] Flash chromatography ("chromatography") used 230-400 mesh silica gel; elution was with hexanes containing an increasing proportion of ethyl acetate. Unless otherwise indicated, yields are for isolated products, homogeneous by GC-MS and by ^{1}H and ^{13}C NMR.

Baker's yeast reductions

Yeast reductions were conducted at 32 °C using a shaking water bath. Baker's yeast was Fleishmann's "Traditional" brand. Fermentation was initiated by shaking (10 min) a suspension of the yeast in an aqueous sucrose solution before the substrate was introduced as a solution in a small amount of 95% ethanol and 0.2% Triton X-100.[9a] Work-up was as follows: diethyl ether was added, the reaction vessel was removed from the shaker, and the mixture was allowed to stand for about 15 h at rt. The mixture was filtered through Celite, and ethyl acetate was passed through the filter cake. The aqueous layer of the filtrate was re-extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was subjected to chromatography to separate the reduction product from unreacted diketone.

Formation of (+)-MTPA esters[12]

The following were introduced through a rubber septum into a dry vial containing approximately 0.1 mmol of a keto-alcohol: dry pyridine (300 μL), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-chloride) (52 μL), and CCl_4 (300 μL). The mixture was allowed to stand at rt for 3 days (to be complete by TLC) before 3-dimethylamino-1-propylamine (50 μL) was introduced. After 5 min, the mixture was diluted with ether. The organic solution was washed with ice-cold 10% aqueous HCl, cold saturated Na_2CO_3, and cold brine. The solution was dried over $MgSO_4$ and then concentrated under vacuum. Samples were analysed by ^{1}H NMR and, in many instances, by ^{13}C or ^{19}F NMR as well.

(4S,5R)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one ((+)-6)

To a suspension of baker's yeast (8.0 g) and sucrose (18 g) in water (100 mL) was added diketone **4** (158 mg, 0.78 mmol) in 3.0 mL of 95% ethanol and 0.2% Triton X-100 (12 mL). The suspension was shaken for 48 h. Work-up provided (+)-**6** as a colorless oil (100 mg, 62%), and 36 mg (23%) of **4** was recovered. For (+)-**6**: $[\alpha]_D$ = +45 (c = 0.0063, MeOH). CD: $[\theta]_{290} \times 10^{-2}$: -9. IR: 3460 (broad), 1730 cm^{-1}. ^{1}H NMR: δ 5.23 (1H, br s), 4.23 (1H, m), 2.64-1.51 (9H, m), 1.64 (3H, s), 1.04 (3H, s), 1.02 (3H, s). ^{13}C NMR: δ 222.0 (0), 131.8 (1), 127.3 (0), 74.5 (1), 54.4 (0), 35.0 (2), 34.8 (2), 33.2 (2), 32.0 (3), 31.2 (0), 30.3 (3), 28.0 (2), 27.3 (3). MS: 208 (53, M$^+$), 193 (13), 175 (87), 149 (78), 133 (86), 131 (32), 121 (42), 119 (55), 107 (50), 105 (38), 91 (62), 81 (32), 79 (34), 77 (37), 55 (47), 53 (33), 43 (74), 41 (100). HRMS calcd for $C_{13}H_{20}O_2$: 208.1462, found: 208.1462.

For the (+)-MTPA ester of **6**: ^{1}H NMR: δ 7.53-7.38 (5H, m), 5.41 (1H, apparent d, J = 3.5 Hz), 5.21 (1H, br s), 3.49 (3H, narrow m), 2.40-2.09 (4H, m), 1.82 (1H, br d, $J \approx$ 16 Hz), 1.70-1.45 (3H, m), 1.63 (3H, s), 0.93 (3H, s), 0.64 (3H, s). ^{13}C NMR: δ 218.8 (0), 165.7 (0), 132.4 (1), 131.6 (0), 129.7 (1), 128.5 (2C, 1), 127.2 (2C, 1), 126.1 (0), 123.3 (q, J = 291 Hz), 80.5 (1), 55.3 (3), 52.9 (0), 34.7 (2), 34.6 (2), 32.8 (2), 32.0 (2), 31.2 (0), 29.5 (3), 25.8 (3), 23.6 (3). ^{19}F NMR: δ -70.73.

(4S,5R)-7,9,9-Trimethyl-4-(trimethylsilyloxy)spiro[4.5]dec-7-ene-1-one ((+)-7)

Chlorotrimethylsilane (0.15 mL, 1.2 mmol) was added to a solution of (+)-**6** (82 mg, 0.39 mmol) in pyridine (2.0 mL) at 0 °C under N_2. The mixture was allowed to warm to rt while it was stirred for 1 h. After addition of CCl_4, the mixture was filtered and concentrated under vacuum. Chromatography provided (+)-**7** (106 mg, 97%) as a colorless solid: mp 75-77 °C. $[\alpha]_D$ = +39 (c = 0.0064, MeOH). CD: $[\theta]_{305} \times 10^{-2}$: -6. IR: 1742 cm^{-1}. ^1H NMR: δ 5.20 (1H, s), 4.12 (1H, t, *J* = 3.7 Hz), 2.40 (1H, m), 2.24 (1H, dd, *J* = 4.1, 8.3 Hz), 2.17-2.01 (2H, m), 1.76-1.69 (3H, m), 1.65 (3H, s), 1.54 (1H, d, *J* = 14.1 Hz), 0.96 (6H, s), 0.13 (9H, s). ^{13}C NMR: δ 221.6 (0), 132.1 (1), 127.5 (0), 75.9 (1), 54.6 (0), 34.9 (2), 34.1 (2), 33.3 (2), 31.5 (0), 31.3 (3), 31.1 (3), 27.9 (2), 23.8 (3), 0.45 (3C, 3). MS: 280 (90, M^+), 175 (58), 164 (19), 149 (23), 133 (24), 129 (29), 107 (16), 91 (18), 75 (28), 73 (100), 41 (19). HRMS calcd for $C_{16}H_{28}O_2Si$: 280.1857, found: 280.1858.

(1R,4S,5R)- ((+)-8a) and (1S,4S,5R)-1,7,9,9-Tetramethylspiro[4.5]dec-7-ene-1,4-diol ((+)-8b)

A stirred solution of (+)-**7** (348 mg, 1.24 mmol) in hexane-ether (1:1) was heated at reflux under N_2, and 2.70 mL of 1.4 M MeLi was introduced. After 10 min methanol (0.15 mL) was added, followed once again by another 2.70 mL of 1.4 M MeLi, until a total of six cycles of MeLi-methanol quench were complete. The mixture was cooled before ether and H_2O were added. The aqueous layer was re-extracted with ether (x4). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was redissolved in CH_2Cl_2 (5.0 mL), and 2.0 mL of 1 M tetrabutylammonium fluoride was added. This was stirred at rt for 3 h. H_2O was added and the aqueous layer was re-extracted with CH_2Cl_2 (x4). The combined organic solutions were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Repeated chromatography provided diols (+)-**8a** (28 mg, 10%) and (+)-**8b** (194 mg, 70%) as colorless oils. For (+)-**8a**: $[\alpha]_D$ = +36 (c = 0.029, $CHCl_3$). ^1H NMR: δ 5.64 (1H, s), 4.19 (1H, t, *J* = 6.6 Hz), 2.92 (1H, s, OH), 2.85 (1H, d, *J* = 6.9 Hz), 2.32-2.21 (2H, m), 1.94-1.85 (2H, m), 1.70-1.63 (4H, m), 1.79 (3H, s), 1.11 (3H, s), 0.96 (3H, s), 0.95 (3H, s). ^{13}C NMR: δ 138.1 (0), 117.3 (1), 85.9 (0), 79.3 (1), 53.5 (0), 44.1 (2), 40.8 (2), 37.4 (2), 32.5 (3), 31.4 (2), 30.8 (0), 27.2 (3), 25.0 (3), 21.7 (3). MS: 206 (56, $M^+ - H_2O$), 191 (32), 173 (29), 163 (24), 149 (100), 133 (30), 121 (56), 107 (51), 93 (30), 85 (38), 69 (23), 55 (34), 43 (98). HRMS calcd for $C_{14}H_{22}O$ ($M^+ - H_2O$): 206.1670, found: 206.1649.

For (+)-**8b**: $[\alpha]_D$ = +98 (c = 0.022, $CHCl_3$). IR: 3361 cm^{-1}. ^1H NMR: δ 5.21 (1H, s), 4.04 (1H, t, *J* = 6.3 Hz), 2.88 (1H, s, OH), 2.58 (1H, d, *J* = 6.3 Hz), 2.19 (1H, m), 1.99-1.66 (5H, m), 1.62 (3H, s), 1.56 (2H, s), 1.19 (3H, s), 1.10 (3H, s), 1.03 (3H, s). ^{13}C NMR: δ 131.6 (1), 128.1 (0), 84.7 (0), 78.0 (1), 51.4 (0), 37.7 (2), 35.4 (2), 33.9 (2), 33.3 (3), 31.9 (0), 31.1 (2), 30.3 (3), 24.1 (3), 21.5 (3). MS: 206 (56, $M^+ - H_2O$), 191 (51), 188 (3), 173 (49), 163 (12), 149 (48), 148 (39), 147 (20), 133 (51), 121 (44), 107 (38), 105 (16), 85 (63), 67 (13), 43 (100). HRMS calcd for $C_{14}H_{22}O$ ($M^+ - H_2O$): 206.1670, found: 206.1675.

(4R,5S)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one ((+)-5)

PCC (250 mg, 1.16 mmol) was added to a solution of a crude mixture of (+)-**8a** and (+)-**8b** (1:7, respectively) (180 mg, 0.873 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 6 h at rt. The mixture was filtered through a pad of silica gel, through which ether was subsequently passed. The combined organic solutions were concentrated under vacuum. Chromatography provided (+)-**5** (107 mg, 69% taking into account that not all of the starting material was (+)-**8b**) as an oil: $[\alpha]_D$ = +12 (c = 0.099, $CHCl_3$). CD: $[\theta]_{300} \times 10^{-2}$: +43. IR, ^1H and ^{13}C NMR, MS and HRMS data were entirely consistent with the data for (±)-**5**.[1]

*8-Methylspiro[4.5]dec-7-ene-1,4-dione (**9**)*

Colorless crystals: mp 76-77 °C (lit.[14] 81.5-83 °C). IR: 1716, 1410 cm^{-1}. ^1H NMR: δ 5.40 (1H, m), 3.00-2.61 (4H, m), 2.13 (2H, sextet, J = 2.1 Hz), 2.02 (2H, apparent t, J = 5.7 Hz), 1.75 (2H, t, J = 6.3 Hz), 1.70 (3H, br s). ^{13}C NMR: δ 214.7 (2C, 0), 132.8 (0), 116.7 (1), 55.1 (0), 34.2 (2C, 2), 27.6 (2), 26.7 (2), 25.7 (2), 23.3 (3). MS: 178 (62, M^+), 149 (25), 136 (22), 135 (100), 121 (34), 107 (31), 94 (21), 93 (35), 91 (45), 57 (21), 55 (43), 51 (29), 43 (24), 41 (39). HRMS calcd for $C_{11}H_{14}O_2$: 178.0993, found: 178.0991.

*(4S,5R)- and (4S,5S)-4-Hydroxy-8-methylspiro[4.5]dec-7-en-1-one ((+)-**10** and (+)-**11**)*

To a suspension of baker's yeast (8.0 g) and sucrose (18 g) in water (100 mL) was added diketone **9** (119 mg, 0.67 mmol) in 3.0 mL of 95% ethanol and 0.2% Triton X-100 (12 mL). The suspension was shaken for 48 h. Work-up provided a 2.6:1 mixture of (+)-**10** and (+)-**11**, respectively, as a colorless oil (89 mg, 74%): $[\alpha]_D$ = +89 (c = 0.0033, MeOH). CD: $[\theta]_{300} \times 10^{-2}$: +15. IR: 3444, 1727 cm^{-1}. For (+)-**10** (from the mixture): ^1H NMR: δ 5.28 (1H, br s, irradiation gave significant NOE's to only: dm, $J \approx$ 17 Hz, at δ 1.95 [1.4%], dm, $J \approx$ 17 Hz, at δ 1.83 [2.6%], s at δ 1.65 [0.7%]), 4.20 (1H, narrow m, irradiation gave 2.1% NOE to the dm at δ 1.83), 2.60-1.50 (13H, m) including a 3H singlet at δ 1.65. ^{13}C NMR: δ 222.0 (0), 134.7 (0), 117.2 (1), 75.1 (1), 52.6 (0), 34.3 (2), 31.1 (2), 28.4 (2), 27.1 (2), 23.3 (3), 22.7 (2).

For (+)-**11** (from the mixture): ^1H NMR: δ 5.44 (1H, br s, irradiation gave no NOE's to signals in the region δ 2.00-1.80), other signals covered by those of **10**. ^{13}C NMR: δ (carbonyl not discerned), 145.0 (0), 119.2 (1), 75.2 (1), 52.5 (0), 34.1 (2), 27.9 (2), 27.8 (2), 26.8 (2), 25.5 (2), 23.3 (3). MS (mixture): 180 (54, M^+), 147 (17), 136 (100), 121 (31), 120 (49), 107 (24), 105 (38), 93 (54), 91 (45), 79 (43), 77 (34). HRMS calcd for $C_{11}H_{16}O_2$: 180.1149, found: 180.1147.

For the (+)-MTPA ester of (+)-**10** (from the mixture of *only two* compounds): ^1H NMR (selected signals): δ 5.39 (1H, apparent d, J = 3.6 Hz), 5.26 (1H, narrow m), 3.53 (3H, narrow m). ^{13}C NMR: δ 219.3, 166.0, 135.0, 132.0, 129.7, 128.5, 127.0, 123.3 (q, J = 289 Hz), 116.2, 80.1, 55.4, 34.2, 31.0, 26.4, 26.0, 23.3, 22.9. ^{19}F NMR: δ -71.40.

For the (+)-MTPA ester of (+)-**11** (from the mixture): ^1H NMR (selected signals): δ 5.46 (1H, apparent d, J = 3.9 Hz), 5.15 (1H, narrow m), 3.52 (3H, narrow m). ^{13}C NMR (clearly discernable signals): δ 218.2, 165.8, 118.8, 79.5, 51.7, 33.9, 27.6, 26.6, 25.7, 25.3, 23.2. ^{19}F NMR: δ -71.92.

*7-Methylspiro[4.5]dec-7-ene-1,4-dione (**12**)*

Oil: IR: 1759 (shoulder), 1721, 1435 cm^{-1}. ^1H NMR: δ 5.54 (1H, m), 3.04-2.69 (4H, m), 2.16 (2H, m), 2.07 (2H, br s), 1.77 (3H, br s), 1.73 (2H, dd, J = 5.1, 6.2 Hz). ^{13}C NMR: δ 214.4 (2C, 0), 130.2 (0), 119.5 (1), 56.3 (0), 34.1 (2C, 2), 30.1 (2), 27.5 (2), 23.2 (3), 21.1 (2). MS: 178 (52, M^+), 149 (21), 135 (48), 121 (35), 94 (27), 93 (40), 91 (53), 79 (100), 78 (20), 77 (77), 67 (26), 65 (35), 57 (20), 55 (50), 53 (47), 43 (45), 42 (27), 41 (48). HRMS calcd for $C_{11}H_{14}O_2$: 178.0993, found: 178.0987.

*(4S,5R)- and (4S,5S)-4-Hydroxy-7-methylspiro[4.5]dec-7-en-1-one ((+)-**13** and (+)-**14**)*

To a suspension of baker's yeast (8.0 g) and sucrose (18.0 g) in water (200 mL) was added diketone **12** (140 mg, 0.79 mmol) in 3.0 mL of 95% ethanol and 0.2% Triton X-100 (12 mL). The suspension was shaken for 48 h. Work-up provided a mixture (1:1) of (+)-**13** and (+)-**14** as a colorless oil (87 mg, 61%) and 27 mg (19%) of **12** was recovered. For this mixture of (+)-**13** and (+)-**14**: $[\alpha]_D$ = +112 (c = 0.0072, MeOH). CD: $[\theta]_{298} \times 10^{-2}$: +18. Some homogeneous (±)-**13** was obtained by crystallization from hexane/ether of the product

of $NaBH_4$ reduction: mp 74-75 °C. IR: 3450 (broad), 1729 cm^{-1}. ^1H NMR: δ 5.49 (1H, br s), 4.20 (1H, br s), 2.53 (1H, br m), 2.32 (1H, dd, J = 3.3, 8.9 Hz), 1.83-1.67 (9H, m including OH), 1.65 (3H, br s). ^{13}C NMR: δ 221.9 (0), 130.3 (1), 121.3 (1), 75.1 (1), 53.2 (0), 35.2 (2), 34.3 (2), 28.2 (2), 23.6 (3), 22.2 (2), 21.9 (2). MS: 180 (51, M^+), 147 (35), 121 (100), 120 (30), 119 (37), 118 (28), 105 (61), 95 (37), 93 (88), 91 (71), 79 (58), 77 (51), 67 (34), 55 (46), 53 (31), 43 (41), 41 (53). HRMS calcd for $C_{11}H_{16}O_2$: 180.1150, found: 180.1152.

For (+)-**14** (from the mixture): ^1H NMR: δ 5.42 (1H, br s), 4.27 (1H, br s), 2.82 (1H, OH), 2.84-2.01 (10H, m), 1.67 (3H, br s). ^{13}C NMR: δ 220.8 (0), 132.8 (0), 119.5 (1), 78.7 (1), 52.5 (0), 33.9 (2), 31.1 (2), 27.6 (2), 26.7 (2), 25.2 (3), 23.2 (2). MS (by GC-MS): essentially the same as for **13**.

For the (+)-MTPA esters of (+)-**13** and (+)-**14** (mixture of *only two* compounds): ^{19}F NMR: δ -71.43, -71.55.

*7,7-Dimethylspiro[4.5]decane-1,4-dione (**15**)*

Oil: IR: 1757 (shoulder), 1722 cm^{-1}. ^1H NMR: δ 2.95 (2H, m), 2.63 (2H, m), 1.82 (2H, m), 1.55 (2H, m), 1.46 (2H, s), 1.34 (2H, m), 0.94 (6H, s). ^{13}C NMR: δ 214.8 (2C, 0), 57.5 (0), 43.0 (2), 37.6 (2), 34.1 (2C, 2), 30.7 (0), 29.3 (2C, 3), 26.0 (2), 17.5 (2). MS: 194 (17, M^+), 179 (6), 151 (4), 138 (15), 137 (8), 125 (100), 97 (20), 95 (29), 81 (22), 79 (24), 69 (52), 67 (33), 56 (20), 55 (57), 53 (33), 43 (26), 41 (87). HRMS calcd for $C_{12}H_{18}O_2$: 194.1306, found: 194.1300.

*(4S,5S)-4-Hydroxy-7,7-dimethylspiro[4.5]decan-1-one ((+)-**16**)*

To a suspension of baker's yeast (6.0 g) and sucrose (16 g) in water (50 mL) was added diketone **15** (47 mg, 0.24 mmol) in 2.0 mL of 95% ethanol and 0.2% Triton X-100 (8.0 mL). The suspension was shaken for 48 h. Work-up provided (+)-**16** as colorless crystals (37 mg, 79%) and 5.0 mg (11%) of **15** was recovered. For (+)-**16**: mp 82-85 °C. $[\alpha]_D$ = +82° (C = 0.0045, MeOH). CD: $[\theta]_{305} \times 10^{-2}$: +5. IR: 3456, 1737 cm^{-1}. ^1H NMR: δ 4.47 (1H, br d, $J \approx 3.3$ Hz), 2.50-1.97 (4H, m), 1.61-1.00 (9H, m), 1.00 (3H, s), 0.98 (3H, s). ^{13}C NMR: δ 222.0 (0), 74.9 (1), 55.1 (0), 38.7 (2), 37.0 (2), 33.4 (2), 33.1 (2), 31.0 (2), 29.6 (0), 27.9 (3), 26.7 (3), 19.2 (2). MS: 196 (11, M^+), 181 (66), 149 (14), 127 (13), 121 (27), 109 (84), 95 (24), 93 (21), 81 (37), 69 (100), 57 (24), 55 (41), 43 (29), 41 (64). HRMS calcd for $C_{12}H_{20}O_2$: 196.1462, found: 196.1462.

For the (+)-MTPA ester of **16**: ^1H NMR: δ 7.55-7.38 (5H, m), 5.65 (1H, br d, J = 3.6 Hz), 3.51 (3H, narrow m), 2.39-2.01 (4H, m), 1.61-0.87 (8H, m), 0.85 (3H, s), 0.62 (3H, s).

*$NaBH_4$ reduction of **18**: (4R*,5S*)- and (4R*,5R*)-4-hydroxy-8,8-dimethylspiro[4.5]dec-6-ene-1-one ((±)-**19** and (±)-**20**)*

$NaBH_4$ (4.0 mg, 0.10 mmol) was added in several small portions to a solution of **18** (78 mg, 0.40 mmol) in methanol (10 mL) at rt. The mixture was stirred for 1 h before H_2O was added, and the mixture was extracted with diethyl ether (x4). The combined organic extracts were washed with H_2O, dried over $MgSO_4$ and concentrated under vacuum. Chromatography of the residue provided a mixture of (±)-**19** and (±)-**20** (3:1, respectively) as a colorless oil (78 mg, 98%). IR: 3472, 1723 cm^{-1}. For (±)-**19** (from the mixture): ^1H NMR (clearly discerned signals only): δ 5.73 (1H, d, J = 9.9 Hz), 5.12 (1H, d, J = 9.9 Hz, irradiation gave a 1.5% NOE at 4.15), 4.15 (1H, narrow m, irradiation gave a 2% NOE at 5.12), 1.03 (3H, s), 0.99 (3H, s). ^{13}C NMR: δ 217.8 (0), 142.7 (1), 122.6 (1), 77.2 (1), 56.3 (0), 34.3 (2), 32.9 (2), 31.5 (0), 29.4 (3), 29.1 (3), 27.0 (2), 19.9 (2).

For (±)-**20** (from the mixture): ^{1}H NMR (clearly discerned signals only): δ 5.87 (1H, *J* = 10.2 Hz), 5.37 (1H, d, *J* = 10.2 Hz), 4.11 (1H, narrow m), 1.03 (3H, s), 1.00 (3H, s). ^{13}C NMR: δ 219.3 (0), 144.2 (1), 119.5 (1), 78.3 (1), 55.9 (0), 34.1 (2), 33.1 (2), 31.5 (0), 29.4 (3), 28.9 (3), 27.9 (2), 26.1 (2). MS (mixture): 194 (60, M^+), 179 (17), 161 (32), 135 (100), 123 (18), 121 (27), 119 (30), 107 (78), 105 (33), 93 (35), 91 (29), 85 (21), 79 (22), 77 (19), 55 (19), 43 (28), 41 (34). HRMS calcd for $C_{12}H_{18}O_2$: 194.1306, found: 194.1308.

Baker's yeast reduction of ***18****: (4S,5R)- and (4S,5S)-4-hydroxy-8,8-dimethylspiro[4.5]dec-6-ene-1-one ((+)-****19*** *and (+)-****20****)*

To a suspension of baker's yeast (10.0 g) and sucrose (22.0 g) in water (200 mL) was added diketone **18** (187 mg, 0.97 mmol) in 4.0 mL of 95% ethanol and 0.2% Triton X-100 (16 mL). The suspension was shaken for 48 h. Work-up provided a mixture (1:1) of (+)-**19** and (+)-**20** as a colorless oil (97 mg, 52%) and 81 mg (43%) of **18** was recovered. For this mixture of (+)-**19** and (+)-**20**: $[\alpha]_D$ = +42 (c = 0.0048, $CHCl_3$). CD: $[\theta]_{308} \times 10^{-2}$: +14. For spectral data, see above.

For the (+)-MTPA esters (mixture of *only two* compounds): ^{1}H NMR (selected signals): δ 7.50-7.41 (m), 5.70 (1H, d, *J* = 10.0 Hz), 5.64 (1H, d, *J* = 10.2 Hz), 5.42 (2H, m), 5.11 (1H, d, *J* = 10.0 Hz), 4.98 (1H, d, *J* = 10.2 Hz), 3.53 (6H, narrow m, both OMe), 1.00 (3H, s), 0.99 (3H, s), 0.95 (3H, s), 0.90 (3H, s). ^{13}C NMR (for both isomers, some signals are coincident): δ 216.8, 215.2, 165.7, 143.1, 143.0, 132.0, 129.7, 128.4, 128.3, 127.2, 127.1, 123.2 (q, *J* = 288 Hz), 120.6, 119.2, 82.4, 80.9, 55.4, 55.0, 54.3, 34.1, 33.8, 32.7, 32.5, 31.5, 31.4, 29.1, 29.0, 26.3, 25.8, 25.1, 20.4. ^{19}F NMR (for both isomers): δ -71.83.

cis-*(4S)-8-*tert*-Butyl-4-hydroxyspiro[4.5]decan-1-one ((+)-****22****)*

To a suspension of baker's yeast (1.0 g) and sucrose (2.5 g) in water (75 mL) was added diketone **21** (51 mg, 0.23 mmol) in 0.4 mL of 95% ethanol and 0.2% Triton X-100 (1.2 mL). The suspension was shaken for 48 h. Work-up provided (+)-**22** as colorless crystals (26 mg, 50%) and 10 mg (26%) of **21** was recovered. For (+)-**22**: mp 135-137 °C. $[\alpha]_D$ = +7 (c = 0.0086, $CHCl_3$). CD: $[\theta]_{300} \times 10^{-2}$: -7. IR: 3409, 1729 cm^{-1}. ^{1}H NMR: δ 3.88 (1H, br t, *J* = 4.8 Hz), 2.42 (1H, m), 2.31-2.15 (2H, m), 1.97-1.80 (2H, m), 1.75 (1H, br, OH), 1.72-1.54 (5H, m), 1.50-1.26 (3H, m), 0.86 (9H, s). ^{13}C NMR: δ 219.9 (0), 79.5 (1), 51.8 (0), 47.7 (1), 34.6 (2), 32.4 (0), 31.5 (2), 27.5 (3C, 3), 27.1 (2), 26.3 (2), 22.5 (2), 22.1 (2). MS: 224 (8, M^+), 209 (7), 206 (9), 168 (23), 167 (32), 150 (29), 149 (18), 108 (34), 107 (34), 81 (32), 79 (21), 67 (24), 57 (100), 55 (30), 41 (58). HRMS calcd for $C_{14}H_{24}O_2$: 224.1775, found: 224.1777.

For the (+)-MTPA ester of **22**: ^{1}H NMR: δ 7.54-7.39 (5H, m), 5.19 (1H, m), 3.53 (3H, narrow m), 2.36 (2H, m), 2.03 (1H, m), 1.76-1.49 (5H, m), 1.37-1.14 (5H, m), 0.83 (9H, s).

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