The Rhodium Carbenoid Route to Cyclic Ethers: Synthesis of the *cis*-2,7-Disubstituted Oxepane Skeleton of Isolaurepinnacin

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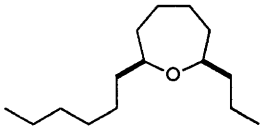
The *cis*-2,7-disubstituted oxepane skeleton **1** of the marine natural product isolaurepinnacin **2** has been obtained by three routes, all of which involve a rhodium(II) acetate mediated cyclisation of diazo alcohols to give the functionalised oxepanes **3**, **4** and **5**, suitable for further elaboration into the common intermediate, the oxepan-3-one **8**.

Natural products containing a medium ring ether system display a fascinating spectrum of structure and biological activity,[1] and not surprisingly, have become popular targets for synthetic organic chemists in recent years.[2] We have previously reported a new route to 2-substituted 3-oxooxepanes based on the rhodium(II) acetate mediated cyclisation of α,ω-diazo alcohols,[3] and we now report in full an application of this methodology to the synthesis of the *cis*-2,7-disubstituted oxepane **1**,[4] which contains the complete carbon skeleton of isolaurepinnacin **2**, a marine natural product isolated from the red alga *Laurencia pinnata*.[5,6]



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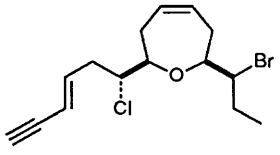

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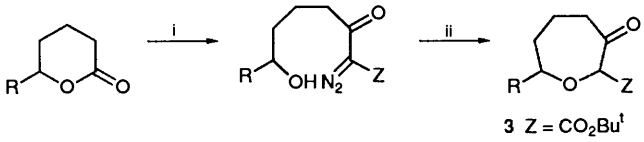
Results and Discussion

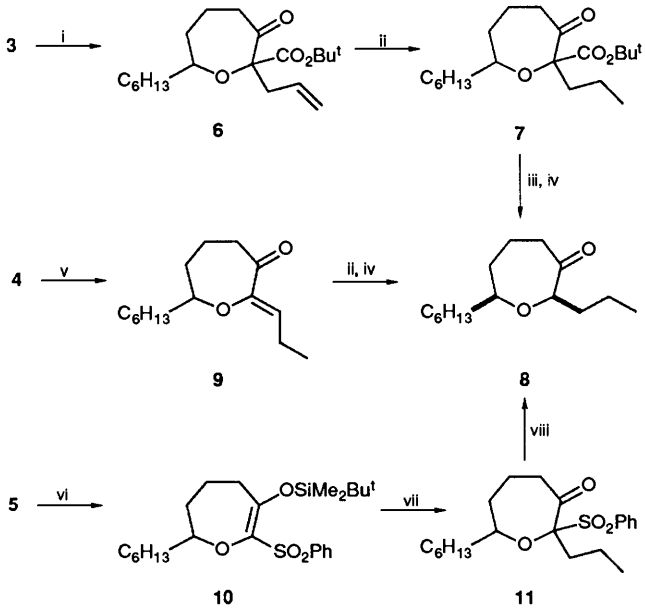
The key intermediate in the synthesis of the *cis*-2,7-disubstituted oxepane **1** was the disubstituted oxepan-3-one **8**, which was prepared by three separate routes from the 3-oxooxepane ester **3**, the phosphonate **4** or the sulphone **5**. These in turn are readily prepared from commercially available undecanoic acid δ-lactone using our previously reported two-step ring expansion of lactones, by ring opening followed by rhodium carbenoid mediated cyclisation (Scheme 1).



3 Z = CO_2Bu^t
4 Z = $PO(OEt)_2$
5 Z = SO_2Ph

Scheme 1 R = C_6H_{13} *Reagents:* i, see ref. 3*d*; ii, cat. $Rh_2(OAc)_4$, benzene

In the first route to the 3-oxepanone **8** (Scheme 2), the β-keto ester **3** was alkylated at the 2-position using organopalladium chemistry.[7] Thus, treatment of the oxepane ester **3** with sodium hydride in tetrahydrofuran (THF) followed by allyl acetate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) gave the oxepane **6** in 86% yield. Catalytic hydrogenation of the double bond to give the oxepane **7**, followed by removal of the unwanted t-butyl ester simply by thermolysis at 150 °C in the presence of a catalytic amount of toluene-4-sulphonic acid[8] gave the desired 2,7-disubstituted oxepan-3-one **8**. The relative stereochemistry of the oxepane **8** is predominantly *cis* (*ca.* 10:1 by ^1H NMR spectroscopy), and treatment with catalytic sodium methoxide in methanol gave the *cis*-isomer **8** exclusively, the stereochemistry of which was confirmed by nuclear Overhauser effect spectroscopy. Thus pre-irradiation of the multiplet at δ 3.09 (7-H) resulted in strong enhancement of the signal at δ 3.70 (2-H), and *vice versa*. The *cis*-isomer is presumably more thermodynamically stable, since the substituents are both pseudo-equatorial in the presumed twist-chair conformation of the seven-membered ring.



6 **7** **8** **9** **10** **11**

Scheme 2 *Reagents:* i, NaH, THF; allyl acetate, $Pd(PPh_3)_4$; ii, H_2 Pd–C, EtOAc; iii, TsOH, heat; iv, NaOMe (cat.), MeOH; v, NaH, THF; EtCHO; vi, Bu^tMe_2SiOTf, Et_3N, CH_2Cl_2; vii, Bu_4NF, THF, PrI; viii, Bu_3SnH, AIBN, toluene

The second route to the oxepan-3-one **8** was from the phosphonate **4** by Wadsworth–Emmons olefination with propionaldehyde to give the enone **9** (72%), followed by catalytic hydrogenation. The reduction gave a mixture of *cis* and *trans* oxepanes in the ratio of 2:1, but epimerisation of the mixture as above gave exclusively the *cis*-diastereoisomer. This second route highlights the use of cyclic β-keto phosphonates in the formation of carbon–carbon bonds at the anomeric position of cyclic ethers, reduction and epimerisation, giving exclusively the *cis*-product. In contrast, use of the benzenesulphonyl group at

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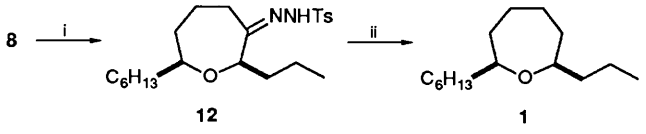
this position in related compounds usually gives the *trans*-disbustituted products.[3d,9]

The use of sulphones was exemplified in the final route to the *cis*-2,7-disubstituted oxepan-3-one **8** from the sulphone **5**. Thus conversion into the silyl enol ether **10** (93%) using t-butyldimethylsilyl trifluoromethanesulphonate (Bu^tMe_2SiOTf), followed by fluoride initiated alkylation with iodopropane gave the β-keto sulphone **11**. This was desulphonylated using the procedure of Smith and co-workers[10] to give the oxepan-3-one **8** as a mixture of isomers, with the *trans*-isomer predominating by a factor of 2:1. Attempts to carry out other sulphone chemistry such as Julia couplings on the oxepane **5** were unsuccessful.[3d]

The oxepan-3-one **8** was finally converted into the *cis*-oxepane **1** by way of its tosyl hydrazone **12** (Scheme 3). Thus, reaction with toluene-4-sulphonohydrazide in methanol, followed by reductive cleavage[11] gave the desired oxepane **1** in 73% yield from the ketone **8**. The oxepane **1** exhibits spectroscopic characteristics consistent with its structure, and with those recently reported.[5a]



Scheme 3 *Reagents:* i, $TsNHNH_2$, MeOH; ii, $NaBH_3CN$, sulpholane, DMF, TsOH, heat

Experimental

For general points, see refs. 3*a* and 3*b*. In addition to these, *J* values are given in Hz.

t-Butyl 7-Hexyl-3-oxo-2-(prop-2-enyl)-oxepane-2-carboxylate **6**.—To a solution of the β-keto ester **3** (1.9 g, 6.38 mmol) in THF (50 ml) at 0 °C under nitrogen was added portionwise over 20 min sodium hydride (60% as dispersion in oil; 280 mg, 7.01 mmol). The mixture was stirred for a further 10 min after which allyl acetate (0.76 ml, 701 mg, 7.01 mmol) and tetrakis (triphenylphosphine)palladium(0) (147 mg, 0.13 mmol) were added sequentially. After the mixture had been stirred for 1 h at 0–5 °C it was poured into water (10 ml) and extracted with ether (2 × 100 ml). The organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography on silica (light petroleum–ether) to give the *title compound* **6** (1.86 g, 86%) as a colourless oil (Found: C, 71.05; H, 10.3. $C_{20}H_{34}O_4$ requires C, 71.0; H, 10.1%); ν_{max}(film)/cm^{-1} 2832, 1738, 1717, 1641, 1369, 1150 and 918; δ(270 MHz; $CDCl_3$) 0.89 [3 H, t, *J* 10, $Me(CH_2)_5$], 1.22–1.34 (6 H, m), 1.45 (9 H, s, Bu^t), 1.43–1.95 (8 H, m), 2.37–2.46 (1 H, ddd, *J* 14, 10, 1.5, 4-C*H*H), 2.57–2.61 (2 H, dd, *J* 11, 1, $CH_2CH{=}CH_2$), 2.70–2.80 (1 H, dt, *J* 16, 3, 4-C*H*H), 3.72–3.82 (1 H, m, 7-CH), 5.02–5.10 (2 H, m, $CH{=}CH_2$), and 5.75–5.90 (1 H, m, $CH{=}CH_2$); *m/z* 338 (M^+), 282, 264, 238, 219, 209, 185, 84 and 57.

t-Butyl 7-hexyl-3-oxo-2-propyloxepane-2-carboxylate **7**.—The oxepane **6** (1.86 g, 5.47 mmol) in ethyl acetate (15 ml) containing 10% palladium on charcoal (180 mg) was hydrogenated at atmospheric pressure for 2 h. The catalyst was filtered off, the filtrate evaporated and the residue passed through a short silica gel column (light petroleum–ether, 20:1) to give the *title compound* **7** in quantitative yield (Found: C, 70.8; H, 10.6. $C_{20}H_{36}O_4$ requires C, 70.55; H, 10.7%); ν_{max}(film)/cm^{-1} 2933, 1739, 1717, 1369, 1149 and 848; δ(270 MHz; $CDCl_3$) 0.82 and 0.94 [6 H, 2t, $Me(CH_2)_5$ and $Me(CH_2)_2$], 1.47 (9 H, s, Bu^t), 1.23–1.90 (18 H, m), 2.36–2.45 (1 H, dd, *J* 14, 10, 4-C*H*H), 2.76–2.87 (1 H, dt, *J* 14, 2.5, 4-C*H*H) and 3.66–3.77 (1 H, m, 7-CH); *m/z* 340 (M^+), 326, 240, 185, 169, 71 and 57.

7-Hexyl-2-propyloxepan-3-one **8**.—The β-keto ester **7** (2.85 g, 5.41 mmol) and toluene-4-sulphonic acid (a few crystals) were heated at 150–160 °C for 10 min, after which the IR spectrum of the crude mixture showed complete disappearance of the ester stretch. The mixture was dissolved in ether–hexane (1:1) and passed through a short pad of silica gel. The eluate was evaporated, and the resulting oil was dissolved in methanol (15 ml). A small amount of sodium metal (~ 10 mg) was added, and the solution stirred at room temperature for 48 h. Aqueous hydrochloric acid (0.5 mol dm^{-3}; 5 ml) was added, the methanol evaporated under reduced pressure and the aqueous mixture extracted with ether (2 × 30 ml). The dried (Na_2SO_4) extract was evaporated and the residue purified by column chromatography on silica (light petroleum–ether) to give the *title compound* **8** (1.22 g, 93%) as a colourless oil (Found: C, 74.9; H, 11.9. $C_{15}H_{28}O_2$ requires C, 75.0; H, 11.7%); ν_{max}(film)/cm^{-1} 2959, 2932, 1714, 1456, 1143 and 1093; δ(270 MHz; $CDCl_3$) 0.83–0.95 [6 H, 2t, *J* 10, $Me(CH_2)_5$ and $Me(CH_2)_2$], 1.25–2.00 (18 H, m), 2.27–2.36 (1 H, ddd, *J* 14, 7, 1.4, 4-C*H*H), 2.85–2.97 (1 H, ddd, *J* 14, 12, 5, 4-C*H*H), 3.09–3.20 (1 H, m, 7-CH) and 3.67–3.74 (1 H, ~dd, *J* 11, 8, 2-CH); *m/z* 240 (M^+), 199, 185, 169, 127, 109, 98 and 84.

7-Hexyl-2-propylideneoxepan-3-one **9**.—To a solution of the β-keto phosphonate **4** (300 mg, 0.98 mmol) in tetrahydrofuran (20 ml) at 0 °C under nitrogen was added sodium hydride (60% as a dispersion in oil; 43 mg, 1.08 mmol). The mixture was stirred for 30 min after which propionaldehyde (78 μl, 63 mg, 1.08 mmol) was added, and the mixture allowed to come to room temperature. It was then stirred for a further 12 h after which it was diluted with water (20 ml) and extracted into ether (2 × 25 ml). The organic extracts were washed with brine (25 ml), dried (Na_2SO_4) and evaporated, and the residue purified by column chromatography on silica (light petroleum–ether) to give the *title compound* **9** (170 mg, 72%) as a colourless oil (Found: M^+, 238.1933. $C_{15}H_{26}O_2$ requires M, 238. 1933); ν_{max}(film)/cm^{-1} 2932, 2860, 1697, 1631, 1329, 1299, 1054 and 863; δ(250 MHz; $CDCl_3$) 0.88 [3 H, t, *J* 14, $Me(CH_2)_5$], 1.05 (3 H, t, *J* 14, $MeCH_2CH$), 1.24–1.42 and 1.44–2.05 (14 H, 2m), 2.24 (2 H, quin, *J* 13.5 $CH{=}CH_2Me$), 2.45–2.55 (1 H, ddd, *J* 10, 7, 1.5, 4-C*H*H), 2.72–2.85 (1 H, dt, *J* 10, 3, 4-C*H*H), 3.37–3.48 (1 H, m, 7-CH) and 5.98 (1 H, t, *J* 13.5, $C{:}CHCH_2$); *m/z* 238 (M^+), 209, 139, 114, 55 and 41.

Hydrogenation of Enol Ether **9**.—The enol ether **9** (140 mg, 0.59 mmol) in ethyl acetate (10 ml) containing palladium on charcoal (14 mg) was hydrogenated at atmospheric pressure for 1 h. The catalyst was filtered off and the solvent evaporated to give the oxepan-3-one **8** as a 2:1 mixture of diastereoisomers in quantitative yield: δ(250 MHz; $CDCl_3$) 0.80–0.90 (6 H, m, 2 × Me), 1.25–2.00 (18 H, m), 2.27–2.36 (1 H, ddd, *J* 14, 7, 1.4, 4-C*H*H, *cis* isomer), 2.52 2.64 (1 H, m, 4-C*H*H, *trans* isomer), 2.70–2.80 (1 H, m, 4-C*H*H, *trans* isomer), 2.85–2.97 (1 H, ddd, *J* 14, 12, 5, 4-C*H*H, *cis* isomer), 3.09–3.20 (1 H, m, 7-CH, *cis* isomer), 3.55–3.64 (1 H, m, 7-CH, *trans* isomer), 3.67–3.74 (1 H, ~dd, *J* 11, 8, 2-CH, *cis*-isomer), 3.84–3.93 (1 H, dd, *J* 11, 4, 2-CH, *trans* isomer); *ca.* 2:1 *cis*:*trans*. Epimerisation of the mixture as described previously gave a single diastereoisomeric ketone **8** which displayed identical spectroscopic characteristics to those already reported.

3-(t-Butyldimethylsiloxy)-7-hexyl-2-phenylsulphonyltetrahydro-4,5,6,7-oxepine **10**.—To a solution of the oxepane **5** (500 mg, 1.48 mmol) in dry dichloromethane (17.5 ml) was added

triethylamine (0.62 ml, 448 mg, 4.44 mmol) followed by t-butyldimethylsilyl trifluoromethanesulphonate (1.02 ml, 1.17 g, 4.44 mmol). The solution was stirred at room temperature under nitrogen for 5 h after which if was diluted with dichloromethane (20 ml), washed with saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated. The residue was purified by passage through a short silica gel column (light petroleum–ether; 20:1) to give the *title compound* **10** (621 mg, 93%) as a colourless oil (Found: M^+, 395.1720. $C_{24}H_{40}O_4SSi - C_4H_9$ requires M, 395.1712); ν_{max}(film)/cm^{-1} 2930, 1625, 1447, 1339, 1322, 1146, 830 and 720; δ(270 MHz; $CDCl_3$) 0.27 (6 H, 2s Me_2Bu^tSi), 0.90 [3 H, ~t, *J* 10, *Me*$(CH_2)_5$], 0.95 (9 H, s, Bu^tMe_2Si), 1.15–1.38 and 1.44–1.90 (14 H, m), 2.09–2.20 (1 H, dd, *J* 14, 5, 4-C*H*H), 2.69–2.80 (1 H, ~dt, *J* 14, 2, 4-C*H*H), 3.45–3.55 (1 H, m, 7-CH) and 7.44–7.58 and 7.90–7.98 (5 H, 2m, ArH); *m/z* 452 (M^+), 395 ($M^+ - C_4H_9$), 271, 253, 199, 147, 135 and 75.

7-Hexyl-2-phenylsulphonyl-2-propyloxepan-3-one **11**.—To a solution of the tetrahydrooxepine **10** (269 mg, 0.60 mmol) in THF (10 ml) at −78 °C under N_2 was added tetrabutylammonium fluoride (1.0 mol dm^{-3} in THF; (0.65 ml, 0.65 mmol). The mixture was stirred for 15 min after which propyl iodide (64 μl, 111 mg, 0.65 mmol) was added and the solution allowed to warm to room temperature overnight. The THF was removed under reduced pressure and the residue triturated with ether. The precipitated ammonium salt was filtered off and the filtrate evaporated. The residue was purified by column chromatography on silica (light petroleum–ether) to give the *title compound* **11** (189 mg, 84%) as a colourless oil (Found: C, 66.4, H, 8.7. $C_{21}H_{32}O_4S$ requires C, 66.3; H, 8.5%); ν_{max}(film)/cm^{-1} 2929, 1718, 1585, 1448, 1300 and 721; δ(270 MHz; $CDCl_3$) 0.79 and 0.90 [6 H, 2t, *J* 10, *Me*$(CH_2)_5$ and *Me*$(CH_2)_2$], 1.25–1.48 and 1.52–2.00 (18 H, 2m), 2.60–2.72 (2 H, m, 4-CH_2), 4.64–4.75 (1 H, m, 7-CH), 7.53–7.70 and 7.95–8.05 (5 H, 2m, ArH); *m/z* 238 ($M^+ - PhSO_2H$), 211, 185, 149, 114, 71 and 43.

Desulphonylation of the β-Keto Sulphone **11**.—Using the procedure described in the preceding paper, the sulphone **11** (189 mg, 0.50 mmol) was desulphonylated using tributyltin hydride (0.54 ml, 582 mg, 2 mmol) and AIBN (160 mg, 0.98 mmol) in toluene (5 ml). Work-up and purification as before gave 7-hexyl-2-propyloxepan-3-one **8** (80 mg, 67%) an approximately 2:1 mixture of *trans*:*cis* isomers, the spectroscopic properties of which corresponded with those already reported.

7-Hexyl-2-propyloxepan-3-one Tosylhydrazone **12**.—The ketone **8** (165 mg, 0.69 mmol), toluene-4-sulphonohydrazide (140 mg, 0.76 mmol) and toluene-4-sulphonic acid (8 mg, 42 μmol) were stirred together in methanol (3 ml) containing powdered 4 Å sieves. After 36 h, the methanol was removed under reduced pressure and the residue diluted with dichloromethane, washed with water (10 ml) and brine (10 ml), dried (Na_2SO_4) and evaporated. The solid residue recrystallized from light petroleum (b.p. 60–80 °C) – ether to give the *title compound* **12** (231 mg, 82%) as a colourless solid, m.p. 114–116 °C (Found: C, 64.4; H, 9.0; N, 6.8. $C_{22}H_{36}N_2O_3S$ requires C, 64.7; H, 8.9; N, 6.8%); ν_{max}($CHCl_3$)/cm^{-1} 2932, 1450, 1352 and 1101; δ(270 MHz; $CDCl_3$) 0.84 [3 H, t, *J* 10, *Me* $(CH_2)_2$], 0.90 [3 H. t, *J* 10, *Me* $(CH_2)_5$], 1.20–1.85 (18 H, m), 2.08–2.22 (1 H, ~dt, *J* 14, 2.5, 4-C*H*H), 2.26–2.37 (1 H, dd, *J* 14, 8, 4-C*H*H), 2.44 (3 H, s, Ar*Me*), 3.00–3.12 (1 H, m, 7-CH), 3.88–3.95 (1 H. dd, *J* 14, 7, 2-CH) 7.42 (1 H, br s, C=NN*H*), 7.28–7.32 and 7.75–7.85 (4 H, 2d, *J* 15, ArH); *m/z* 408 (M^+), 366, 253, 211, 99, 91, 71 and 43.

(2S*,7R*)*2-Hexyl-7-propyloxepane* **1**.—To a solution of the tosylhydrazone **12** (300 mg, 0.74 mmol) in dimethylformamide (2 ml) and sulpholane (2 ml) at 110–120 °C was added in one portion sodium cyanoborohydride (186 mg, 2.96 mmol) and toluene-4-sulphonic acid (40 mg, 0.21 mmol). Three further identical portions of sodium cyanoborohydride and toluene-4-sulphonic acid were added at 3 hourly intervals, and then heating continued for a further 12 h. The reaction mixture was extracted into pentane (4 × 10 ml) and the organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml), dried (Na_2SO_4), evaporated. The residue was purified by column chromatography on silica (hexane–ether) to give the *title compound* **1** (145 mg, 87%) as a colourless oil, ν_{max}(film)/cm^{-1} 2929, 1357, 1141 and 1101; δ(270 MHz; $CDCl_3$) 0.82–0.94 (6 H, m, 2 × Me), 1.20–1.40 (11 H, m), 1.40–1.58 (7 H, m), 1.60–1.79 (4 H, m) and 3.30–3.42 (2 H, m, 2-CH and 7-CH); δ_C(125 MHz; $CDCl_3$) 14.10, 19.47, 22.64, 25.31, 25.34, 25.96, 26.27, 29.34, 31.89, 36.87, 36.92, 37.44, 39.64, 80.03 and 80.33; *m/z* 226 (M^+), 183, 165, 141, 123, 97, 55, and 43.

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