Two Contrasting Asymmetric Approaches to Muscarine Based on 5-*endo*-trig Cyclisations

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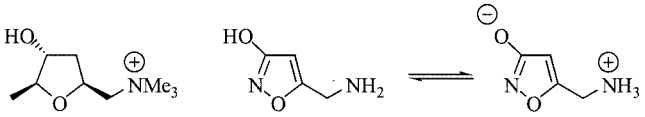
5-*endo*-trig cyclisation of the (*Z*)-hydroxyalkenoate **17** using iodine as the electrophile gave a good yield of the β-hydroxytetrahydrofuran **18**, probably via the corresponding iodohydrin. A variety of one-carbon degradation methods were then used to generate precursors to (–)-muscarine (**25d**). An alternative strategy featured control of a 5-*endo*-trig iodocyclisation by an allylic hydroxyl group, which can be used for the highly stereocontrolled synthesis of hydroxy-iodotetrahydrofurans **28**. Application of this strategy to the (*Z*)-alkenediol derivative **38** led to an excellent yield of the tetrahydrofuran **39** when iodine monobromide was used as the electrophile. Two simple and efficient transformations then gave the (+)-muscarine precursor **40b**.

Introduction

(+)-Muscarine (**1**) is a major toxic principle of the well-known Fly agaric mushroom, *Amanita muscaria*, a common and spectacular (if dangerous) feature of autumnal woodlands.[1] It is, however, not the only biologically active alkaloid present in this species, because it occurs alongside muscimol (**2**). This latter, seemingly simple compound is responsible for the hallucinogenic effects of the mushroom, a property used in ancient rituals by shamen and in South American Indian cults of mushroom worship.[2] Muscarine alkaloids are found in many other species of mushroom including other members of the genus *Amanita*, such as the Death cap, *A. phalloides*, along with many *Inocybes* and *Clitocybes* species.[1] Many of these compounds are stereoisomers of the muscarine structure **1** and include (−)-(2*S*,3*R*,5*R*)-allomuscarine (**3**), (+)-epimuscarine [the (2*S*,3*S*,5*S*)-isomer], and (+)-epiallomuscarine [the (2*S*,3*S*,5*R*) isomer].[3] Muscarine itself has a long and noble history stretching back to 1811, when the first recorded attempts at its structural determination and synthesis were made.[4] Despite its structure being uncertain at the time, it even achieved literary fame in 1930, when the difference between "synthetic" and natural muscarine held the key to a murder mystery.[5]



(L)-(+)-Muscarine 1 **Muscimol 2**

Early work on muscarine (**1**) was plagued by purification problems, and many samples were contaminated with choline and acetylcholine, which were also present in the fungal source.[6] Pure material was eventually secured in 1954[7] and its structure firmly established by X-ray crystallographic analysis,[8] thus opening up a new era of investigations into its synthesis and pharmacological activity. The action of muscarine upon smooth muscle so resembles that of acetylcholine (**4**) that direct action on cholinergic receptors in the autonomic nervous system has come to be known as "muscarinic" action.[3]

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Many muscarinic subtypes have subsequently been identified,[9] and its acetylcholine agonistic activity has many potential applications in a variety of medicinal therapies, notably neurodegenerative conditions such as Parkinson's and Alzheimer's diseases.[10] Amongst the known muscarine isomers (see above), muscarine (**1**) itself displays the most potent biological activity and can adopt a conformation close to that preferred by acetylcholine (**4**) in solution.[3,8,11] These potent biological activities, together with its relatively simple but arguably somewhat awkward structure, have re-

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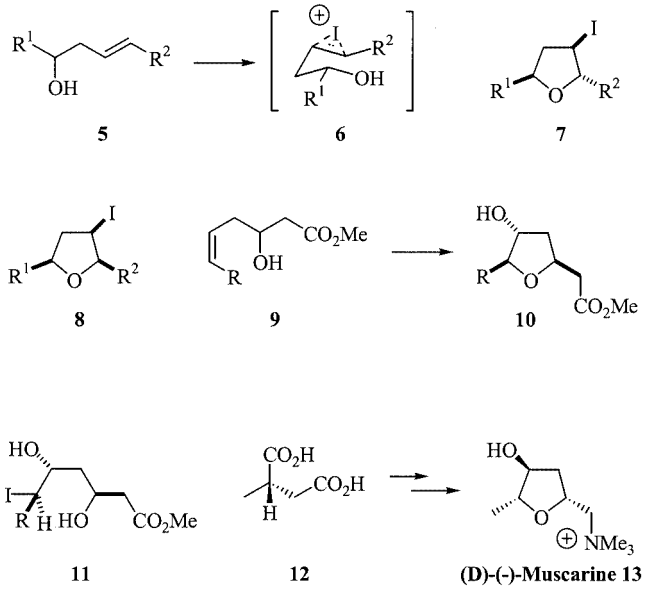
sulted in muscarine becoming something of a test bed for new synthetic methodologies or strategies and hence a number of total syntheses have been published to date. Perhaps inevitably, the presence of a number of C−O bonds in muscarine suggests carbohydrate precursors. Examples of this idea include the first, short (but non-regioselective) approach from L-glucosamic acid[12] and a subsequent synthesis by the same group starting from 2-deoxy-D-ribose.[13] An alternative began with 2-deoxy-L-ribose;[14] approaches from D-mannitol,[15] isopropylidene glyceraldehyde,[16] D-glucose,[17] and D-mannonolactone[18] each have notable features and some the flexibility to prepare other muscarine isomers or homologues. Arguably, one of the most practical is a more recent approach from L-rhamnose.[19] Various contrasting cyclisation methods to establish the tetrahydrofuran ring have also been reported, including diazo displacement by a suitably positioned hydroxyl group,[20] chelation-controlled Grignard addition to an α-acetoxy-aldehyde and tosylate displacement[21] and very short approaches based on 5-*exo*-trig iodocyclisations,[22] which were also a key feature of Mulzer's methodology.[16] A very recent synthesis of some muscarine isomers features [3+2] cycloadditions between crotylsilanes and α-silyloxyaldehydes.[23] Other approaches have utilised cyclobutanone ring expansion,[24] dihydrofuran hydroboration,[25] and carbenoid insertion into a C−H bond α to an ether oxygen[26] to establish the necessary tetrahydrofuran ring. Lengthier routes begin with (*Z*)-5-hydroxymethyl-2(5*H*)-furanone[27] or a 4-oxo-tetrahydrofuran-2-carboxylate.[28] Stereoisomers[29] and homologues,[30] some of which possess high levels of bioactivity, have also been prepared. Finally, Overman has applied his elegant acid-catalysed rearrangement of allylic diols to a synthesis of a key diol precursor to muscarine,[31] which forms the subject of the latter part of this paper.

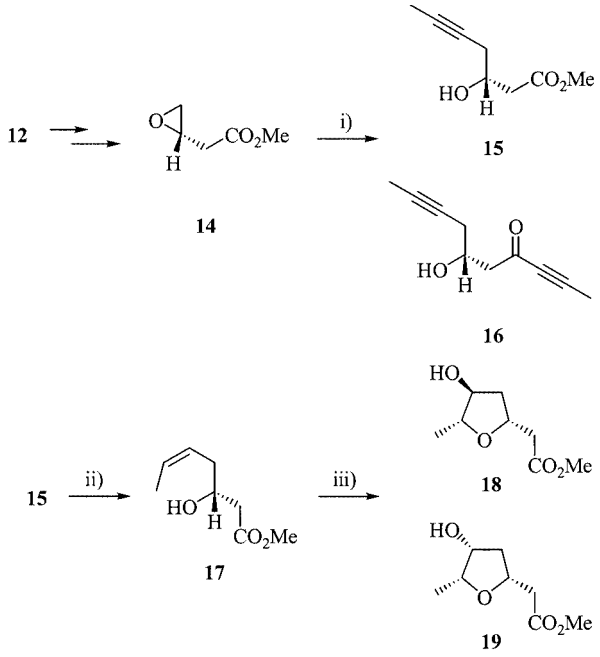


Herein, we give a full account of two contrasting asymmetric approaches to muscarine (**1**), both of which feature applications of overall 5-*endo*-trig cyclisations recently highlighted by us as useful synthetic methods. In our earlier model studies,[32] we had established that (*E*)-homoallylic alcohols (**5**; R^1, R^2 = alkyl, aryl) undergo very smooth 5-*endo*-trig iodocyclisations when treated with three equivalents each of iodine and sodium hydrogencarbonate in acetonitrile under strictly anhydrous conditions to give excellent yields of the iodotetrahydrofurans **7**. The transition state conformation **6** appears to account for this stereochemical outcome. Examples of the corresponding (*Z*)-homoallylic alcohols similarly gave the *all-cis*-iodotetrahydrofurans **8**, albeit in much poorer yields and much more slowly, probably due to a more crowded and hence less favourable transition state. However, a surprise came with the finding that, in the special case of the (*Z*)-unsaturated β-hydroxy esters **9**, the products were largely the hydroxytetrahydrofurans **10**, rather than the expected iodotetrahydrofurans. An explanation for this[33] features participation by the ester group and subsequent regio- and stereoselective formation of the iodohydrins **11** and a final, slow cyclisation by iodide displacement. Certainly, iodohydrins can be isolated during the early stages of the reaction, but full characterisation was precluded by their propensity to undergo cyclisation. This relatively rapid and efficient formation of the hydroxytetrahydrofurans **10** suggested that this methodology could be suitable for a relatively efficient synthesis of muscarine (**1**).[34]

Results and Discussion

For reasons of economy, we chose to use (*S*)-malic acid (**12**) as our starting material, which we planned would lead to (−)-muscarine (**13**). The diacid **12** was efficiently converted into the epoxybutanoate **14** using the method of Larchevêque.[35] Subsequent alkylation of lithiopropyne[36] by this epoxide under Yamaguchi−Hirao conditions[37] then delivered an excellent yield of the hydroxyheptynoate **15**, with the only significant impurity being 5−10% of the easily separated double addition product **16** (Scheme 1).

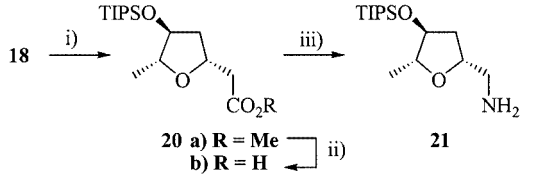
Lindlar reduction proceeded smoothly to give the necessary (*Z*)-hydroxyalkenoate **17**, which proved to be rather photosensitive with respect to isomerisation to the corresponding (*E*)-isomer. As expected, the key "iodocyclisation" step then gave a respectable 63% isolated yield of the desired hydroxytetrahydrofuran **18**, whose structure and stereochemistry were established as described previously.[32,33] Also isolated (in an 11% yield) was the epimeric hydroxytetrahydrofuran **19**, which is presumably formed by non-selective iodohydrin generation. Traces of iodotetrahydrofuran(s) were also detected which probably arose due to a small amount of (*Z*)→(*E*) isomerisation prior to or during the cyclisation step. The hydroxyl group of the major product **18** was then protected as a robust TIPS ether, and the resulting derivative **20a** saponified to give the corresponding carboxylic acid **20b**. Earlier experiments with the corresponding TBDMS derivative indicated that this group was not sufficiently stable during the ester



Scheme 1. i) Lithiopropyne, $BF_3{\cdot}OEt_2$, THF, −78 °C, 4 h, 80% **15** + 5−10% **16**; ii) H_2 (1 atm.), 5% Pd-$BaSO_4$, quinoline, EtOAc, 0.75 h, 87%; iii) I_2, $NaHCO_3$, MeCN, 0−5 °C, 72 h, 63% **18** + ca. 11% **19**

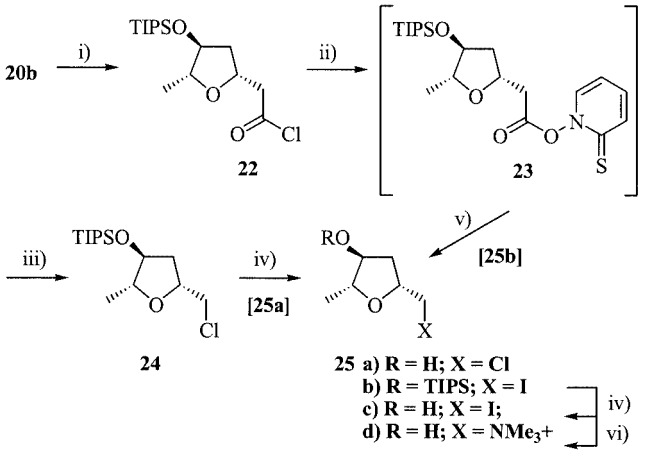
saponification step to be of use. At no stage was any epimerisation observed, which could conceivably occur by a *retro*-Michael ring opening-reclosure mechanism.

To complete the synthesis, it was necessary to carry out a one-carbon degradation of the acetic acid side chain. For this, a most convenient and efficient procedure appeared to be Curtius degradation which was expected to provide the aminomethyl derivative **21** (Scheme 2). Although the reaction sequence using diphenylphosphoranyl azide[38] followed by isocyanate hydrolysis and *N*-methylation was apparently successful, it gave a sample of *O*-TIPS muscarine which proved difficult to purify, despite a report[24] that this conversion sequence could be achieved in good yield in the cases of some related derivatives.



Scheme 2. i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 74%; ii) KOH, MeOH/H_2O, 20 °C, 16 h, 97%; iii) $(PhO)_2P(O)N_3$, Et_3N, toluene, 80 °C, 2 h then H_2O, 20 °C, 16 h, 90%

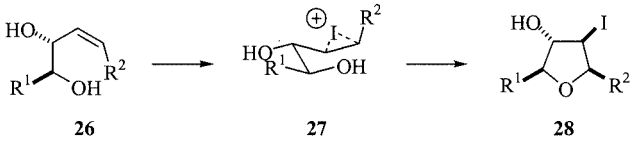
Because other *N*-methylation methods (e.g. $NaBH_3CN$/formaldehyde)[39] were less efficient, we turned to an alternative one-carbon degradation method — the Barton−Hunsdiecker reaction[40] — which, if successful, would allow introduction of the required amine function in the final step, and lead directly to a muscarine salt without the need for a potentially difficult purification. Hence, the carboxylic acid **20b** was converted into the corresponding acid chloride **22** using oxalyl chloride and catalytic DMF [for these experiments, racemic samples were used, derived for convenience from more readily available (±)-methyl 3,4-epoxybutanoate] (Scheme 3). Simply adding the acid chloride **22** to a refluxing suspension of the sodium salt of 2-mercaptopyridine *N*-oxide led to the rapid formation of the intermediate thiohydroxamic ester **23**, and thence to the desired chloride **24** in very good overall yield. Subsequent deprotection using fluoride proceeded smoothly to give the penultimate muscarine precursor **25a**. Unfortunately, this proved to be insufficiently reactive with trimethylamine; heating in a sealed tube at 130 °C resulted in extensive decomposition. Presumably, this is a manifestation of the β-halo ether deactivating effect, exacerbated by the presence of the hydroxyl group, which renders the substrate more thermally sensitive. This is in contrast to the parent tetrahydrofurfuryl chloride, which does react smoothly with trimethylamine at 130 °C.[41] We therefore returned to the Barton−Hunsdiecker step and used iodoform as the initial radical source, with cyclohexene as both a solvent and halogen trap.[40] This proved to be successful, if not quite so efficient, and delivered the known hydroxy iodide **25c**, following fluoride-induced desilylation of the initial product **25b**. We were pleased to find that the hydroxy iodide **25c** exhibited analytical and spectroscopic data which were identical to those previously reported,[16,22] except for the sign of rotation. Finally, exposure to trimethylamine in ethanol at 70 °C delivered, as expected,[16] a sample of D-(−)-muscarine iodide (**25d**), which was also identical to the material prepared previously, except for the sign of rotation.



Scheme 3. i) $(COCl_2)$, DMF (cat.), pyridine, C_6H_6, 0 °C, 3 h; ii) 2-mercaptopyridine *N*-oxide sodium salt, DMAP (cat.), CCl_4; iii) 65 °C, 1.5 h, 73% from **20b**; iv) TBAF, THF, 20 °C, 40 h, 60%; v) as ii) but CHI_3 in place of CCl_4 and reflux in cyclohexene for 15 h, 60% from **20b**; vi) Me_3N, EtOH, 70 °C, 4 h (sealed tube), 75%

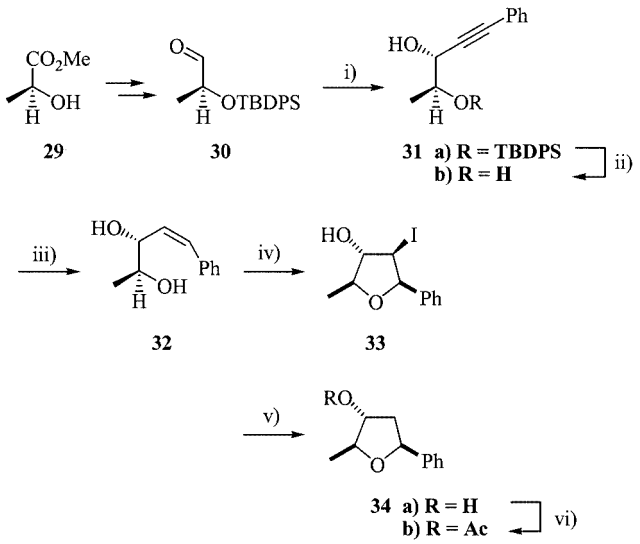
Overall, this approach is a relatively short one, which certainly has some potential for the synthesis of analogues by, for example, using homologous 1-alkynes for the formation of the precursor hydroxy esters (cf. **15**). Clearly, the natural (+)-stereoisomer could be obtained simply by starting with

(*R*)-malic acid or the enantiomer of the epoxy ester **14**, obtained by a different route. However, the lack of complete stereocontrol in the key cyclisation step leading to hydroxytetrahydrofuran **18**, together with a relatively poor yield of the iodide **25b** and the five-step synthesis of epoxy ester **14**,[35] led us to contemplate an alternative approach based on the 5-*endo*-trig cyclisation strategy. The precise tactics for this were evident from our more recent findings regarding the control of such cyclisations by hydroxyl groups. Of particular relevance to the present target was the observation that iodocyclisations of the (*Z*)-*anti*-alkene diols **26** delivered excellent yields of (very largely) the iodotetrahydrofurans **28**, presumably via the transition state conformation **27**.[42] Such efficient cyclisations are in direct contrast to the much poorer returns from similar reactions of simpler (*Z*)-homoallylic alcohols, to give the *all-cis* iodotetrahydrofurans **8**. As our model studies had featured only simple alkyl and aryl substituents, a concern was whether this methodology could be extended to cases where the products were tetrahydrofuran-2-methanol derivatives (i.e. **28**; $R^2 = CH_2OR$), and the related issue of defining suitable protecting groups. Indeed, our first attempt to apply this methodology avoided the latter consideration by having R^2 = Ph, in the hope that a late oxidative degradation might deliver the required one-carbon side chain.



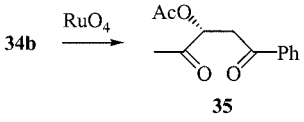
Fortunately, a suitable starting material for this approach was cheap methyl (*S*)-lactate (**29**) which, it was hoped, would deliver (+)-muscarine (**1**). Thus, ester **29** was converted in two very efficient steps into the known *O*-silyl lactaldehyde **30**.[43] Crucially, non-chelation controlled addition[44] of lithiated phenylacetylene in the presence of 12-crown-4 gave an excellent yield of the *anti*-stereoisomer **31a**, containing approximately 11% of the corresponding *syn*-isomer (Scheme 4). Desilylation and Lindlar reduction then gave the (*Z*)-alkene diol **32**, which subsequently underwent iodocyclisation to give a respectable yield of stereopure iodotetrahydrofuran **33**. The alkene diol **32** proved to be quite water-soluble, and much material was lost during the removal of residual quinoline (used in the reduction step) by an aqueous acid wash.

Fortunately, the presence of this base did not appear to have a deleterious effect upon the subsequent iodocyclisations, thereby obviating the need for an acid wash. The stereochemistry of the heterocycle **33** was secured as described previously, and determined by comparisons with related data.[32,33] Initially, the necessary iodine removal was carried out using the tri-*n*-butyltin hydride-AIBN method[40b] but the inevitably tedious purification led us to seek alternatives, despite obtaining workable 60−70% yields of the desired product **34a**. Fortunately, we found that hydrogenolysis[45] of the iodotetrahydrofuran **33** in the presence



Scheme 4. i) Lithiophenylacetylene, 12-crown-4, THF, −78 °C to 0 °C, 4 h, 76% (+ 11% of the syn-isomer); ii) TBAF, THF, 20 °C, 2 h, 93%; iii) H_2 (1 atm.), 5% Pd-$CaCO_3$, quinoline, hexane/2% MeOH, 20 °C, 2 h; iv) I_2, $NaHCO_3$, MeCN, 0 °C, 4 h, 51% from **31b**; v) H_2 (1 atm.), 10% Pd-C, Et_3N, EtOAc, 20 °C, 16 h, 98%; vi) Ac_2O, pyridine, 20 °C, 16 h, 97%

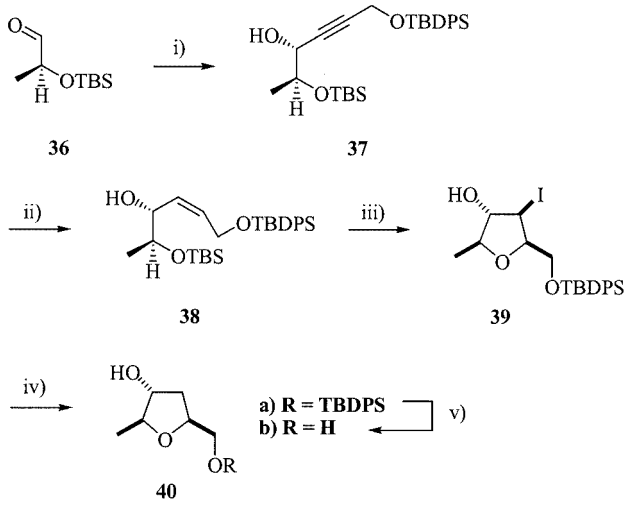
of triethylamine, followed by a simple filtration, resulted in an essentially quantitative yield of the de-iodinated product **34a**. Conversion into the corresponding acetate **34b** proceeded smoothly. Sadly, however, exposure of the latter to ruthenium tetroxide using the now standard Sharpless conditions[46] led to a high yield of the dione **35** (Scheme 5). No products arising from attack on the phenyl ring were in evidence.[47] Ozonolysis under various conditions destroyed the molecule. Clearly, oxidation of the α-positions of the tetrahydrofuran ring takes precedence over cleavage of the phenyl group.



Scheme 5

We therefore examined the prospects for employing a propargyl alcohol derivative,[48] and were glad to find that a non-chelation controlled addition[44] of lithiated *O*-TBDPS propargyl alcohol to *O*-silyl lactaldehyde **36**[43] gave the desired *anti* adduct **37** in excellent yield and with a very usable level of stereoselection (ca. 9:1 *anti*/*syn*) (Scheme 6). Subsequent Lindlar reduction then gave the corresponding (*Z*)-alkene **38** in excellent yield. Optimisation experiments revealed that, although this derivative could be selectively deprotected, this was unnecessary as iodocyclisation with loss of the *O*-TBS group took place readily when the (*Z*)-alkene **38** was exposed to three equivalents of iodine as usual. Even better yields (up to 70%) of the desired iodotetrahydrofuran **39** were secured by direct treatment of **38** with two equivalents of iodine monobromide in acetonitrile at −10 °C. For-

tunately, the product(s) arising from *syn*-**38** could be separated easily at this stage. Completion of the synthesis then followed the pathway described above; hydrogenolysis provided an excellent yield of the de-iodinated tetrahydrofuran **40a**, desilylation of which gave the diol **40b**. This latter compound, which showed analytical, rotational and spectroscopic data identical to those previously reported[19] has previously been converted into (+)-muscarine (**1**) in two straightforward steps. Hence, this final approach represents a formal synthesis of the natural target.



Scheme 6. i) LiC≡CCH$_2$OTBDPS, 12-crown-4, THF, −78 °C to 0 °C, 4 h, 65% (+ 9% of the *syn* isomer); ii) H_2 (1 atm.), 5% Pd-$CaCO_3$, quinoline, MeOH, 20 °C, 0.25 h, 90%; iii) IBr, $NaHCO_3$, MeCN, −10 °C, 3.5 h, 68%; iv) H_2 (1 atm.), 10% Pd-C, Et_3N, EtOAc, 20 °C, 16 h, 91%; v) NH_4F, MeOH, 20 °C, 16 h, 56%

Conclusions

Three relatively short approaches to enantiomers of muscarine (**1**) have been developed. The shortest begins with methyl (*S*)-lactate and is complete in 9 steps, many of which are simple and high yielding.

Experimental Section

General Remarks: NMR spectra were recorded using Bruker WM or DPX spectrometers, operating at 250 MHz or 400 MHz, respectively for ^{1}H spectra and at 67.5 MHz or 100.6 MHz, respectively for ^{13}C spectra. Unless stated otherwise, NMR spectra were measured using dilute solutions in $CDCl_3$. All NMR measurements were carried out at 30 °C, and chemical shifts are measured relative to tetramethylsilane (δ = 0.00 ppm) or to the resonances of $CDCl_3$ (δ = 7.27 ppm for ^{1}H and δ = 77.0 ppm (the central line of the triplet) for ^{13}C). Low resolution mass spectra were obtained using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionisation (ApcI) modes, as stated. High resolution mass spectrometry was performed by the EPSRC Mass Spectrometry Service, University College, Swansea, using the ionisation modes specified. Optical rotations were measured using a JASCO DIP 370 polarimeter. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin−Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solution from aqueous workups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. Column chromatography was carried out using Merck Silica Gel 60 (230−400 mesh). TLC analyses were carried out using Merck silica gel 60 F254 pre-coated, aluminium-backed plates, which were visualised using potassium permanganate or ammonium molybdenate sprays or ultraviolet light.

Methyl (*R*)-3-Hydroxyhept-5-ynoate (15): Propyne (ca. 8 mL) was condensed under an atmosphere of dry nitrogen, dissolved in anhydrous THF (60 mL) and the solution cooled to −78 °C before the addition of *n*BuLi (21.5 mL of a 1.6 M solution in hexanes, 34.4 mmol). The resulting solution was stirred at this temperature for 0.5 h, and boron trifluoride diethyl etherate (2.83 mL, 23 mmol) added. After a further 10 min, methyl (*S*)-3,4-epoxybutanoate (**14**)[35] (2.64 g, 23 mmol) was added. After stirring for a further 4 h at −78 °C, the solution was poured into saturated aqueous ammonium chloride (200 mL) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic solutions dried and evaporated to leave a pale yellow oil which was chromatographed over silica gel (15% diethyl ether in petroleum ether) to give the *alkynol* **15** (2.90 g, 80%) as a colourless oil. $[\alpha]_D^{24}$ = −13.2 (*c* = 7.1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79 (t, *J* = 2.6 Hz, 3 H, 7-CH_3), 2.38−2.40 (m, 2 H, 4-CH_2), 2.47 (dd, *J* = 16.2, 8.6 Hz, 1 H, 2-H_a), 2.71 (dd, *J* = 16.2, 3.8 Hz, 1 H, 2-H_b), 3.71 (s, 3 H, OCH_3), 4.12−4.20 (m, 1 H, 3-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 13.2 (7-CH_3), 26.5 (4-CH_2), 39.9 (2-CH_2), 51.6 (OCH_3), 66.7 (3-CH), 74.3 (C), 78.4 (C), 172.7 (C = O) ppm. IR (film): ṽ = 3452, 2221, 1736, 1672, 1439, 1162, 1059 cm^{-1}. MS (EI): *m*/*z* = 138 [M^+ − H_2O, 7%], 103 (100), 81 (15), 71 (56), 61 (22). HRMS: calcd. for $C_8H_{10}O_2$ 138.0681, found 138.0685.

Methyl (3*R*,5*Z*)-3-Hydroxyhept-5-enoate (17): Quinoline (58 μL) was added to a suspension of 5% palladium on barium sulfate (63 mg) in anhydrous ethyl acetate (2 mL). The suspension was stirred for 10 min before addition of the alkynol **15** (0.33 g, 2.1 mmol) in ethyl acetate (2 mL). Stirring was continued under a hydrogen atmosphere, with complete protection from light, until gas absorption virtually ceased (ca. 0.75 h). The mixture was filtered through Celite, the combined filtrate and washings washed with 1 M hydrochloric acid (10 mL), saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried, and the solvents evaporated to leave the (*Z*)-*alkene* **17** (0.29 g, 87%) as an oil. $[\alpha]_D^{23}$ = −22.7 (*c* = 2.7, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.84 (dd, *J* = 7.3, 0.5 Hz, 3 H, 7-CH_3), 2.45−2.35 (m, 2 H, 4-CH_2), 2.52 (dd, *J* = 16.2, 8.7, 2-H_a), 2.76 (dd, *J* = 16.2, 3.9 Hz, 2-H_b), 3.25 (d, *J* = 4.2 Hz, 1 H, OH), 3.73 (s, 3 H, OCH_3), 4.12−4.21 (m, 1 H, 3-H), 5.40−5.46 (m, 1 H), 5.61−5.67 (m, 1 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 13.0 (7-CH_3), 34.2 (4-CH_2), 40.7 (2-CH_2), 51.8 (OCH_3), 68.0 (3-CH), 125.4 (5-CH), 127.2 (6-CH), 173.3 (C = O) ppm. IR (film): ṽ = 3417, 1732, 1438, 1371, 1259, 1202, 1163, 1058 cm^{-1}. MS (EI): *m*/*z* = 140 [M^+ − H_2O] (11%), 103 (100), 81 (22), 71 (95), 61 (41). HRMS: calcd. for $C_8H_{12}O_2$ 140.0837, found 140.0846.

Methyl (2*R*,4*S*,5*R*)-(4-Hydroxy-5-methyltetrahydrofuran-2-yl)acetate (18): Sodium hydrogen carbonate (0.81 g, 9.6 mmol) was added to an ice-cold solution of the (*Z*)-alkene **17** (0.45 g, 3.2 mmol) in

anhydrous acetonitrile (7 mL) and the suspension stirred for 5 min. Solid iodine (2.44 g, 9.6 mmol) was added and the resulting mixture stirred at 0−5 °C for 72 h, with the exclusion of light. Diethyl ether (30 mL) was added and the mixture washed with saturated aqueous sodium thiosulfate (120 mL). The separated aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic solutions were dried and evaporated and the residue filtered through a plug of silica with the aid of diethyl ether to give the hydroxytetrahydrofuran **18** (0.35 g, 63%) as a colourless oil. $[\alpha]_D^{22} = +14.8$ (c = 0.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.87 (ddd, J = 13.2, 9.4, 6.4 Hz, 1 H, 3-H_a), 2.02 (ddd, J = 13.2, 6.0, 2.6 Hz, 1 H, 3-H_b), 2.52 (dd, J = 15.6, 6.2 Hz, 1 H, 1′-H_a), 2.66 (dd, J = 15.6, 6.9 Hz, 1′-H_b), 3.69 (s, 3 H, OCH_3), 3.87 (qd, J = 6.4, 3.4 Hz, 1 H, 5-H), 4.00−4.03 (m, 1 H, 2-H), 4.47 (ddd, J = 9.4, 6.0, 3.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 19.8 (5-CH_3), 40.5 (3-CH_2), 40.7 (1′-CH_2), 51.7 (OCH_3), 74.0 (2-CH), 77.2 (4-CH), 82.1 (5-CH), 173.3 (C = O) ppm. IR (film): $\tilde{\nu}$ = 3402, 1734, 1440, 1371, 1163, 1078 cm^{-1}. MS (EI): m/z = 156 [$M^+ - H_2O$] (5%), 101 (51), 98 (100), 74 (57), 57 (61). HRMS: calcd. for $C_8H_{12}O_3$ 156.0786, found 156.0791. $C_8H_{14}O_4$: calcd. C 55.17, H 8.05; found C 55.44, H 8.16.

Methyl (2*R*,4*S*,5*R*)-[5-Methyl-4-(triisopropylsilyloxy)tetrahydrofuran-2-yl]acetate (20a): 2,6-Lutidine (0.154 g, 1.44 mmol) was added to a stirred solution of the hydroxytetrahydrofuran **18** (0.10 g, 0.57 mmol) in anhydrous dichloromethane (1.6 mL) at 0 °C. Triisopropylsilyl trifluoromethanesulfonate (0.23 mL, 0.86 mmol) was added dropwise and the resulting mixture stirred at this temperature for 3 h. Brine (20 mL) was then added and the resulting mixture extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried, the solvents evaporated, and the residue chromatographed on silica gel (7% EtOAc in petroleum ether) to give the *silyl ether* **20a** (0.14 g, 74%) as a colourless oil, $[\alpha]_D^{20} = +16.2$ (c = 1.6, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.09−1.11 (m, 21 H), 1.27 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.80 (ddd, J = 13.6, 9.3, 6.4 Hz, 1 H, 3-H_a), 2.05 (ddd, J = 13.6, 5.9, 2.7 Hz, 1 H, 3-H_b), 2.54 (dd, J = 15.3, 6.6 Hz, 1 H, 2-H_a), 2.65 (dd, J = 15.3, 6.4 Hz, 1 H, 2-H_b), 3.67 (s, 3 H, OCH_3), 3.85 (qd, J = 6.4, 3.1 Hz, 1 H, 5-H), 4.05 (ddd, J = 6.4, 3.1, 2.7 Hz, 1 H, 4-H), 4.50 (dddd, J = 9.3, 6.6, 6.4, 5.9 Hz, 1 H, 2 -H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.0 (6 × CH_3), 17.9 (3 × CH), 19.9 (5-CH_3), 40.6 (3-CH_2), 41.2 (1′-CH_2), 51.6 (OCH_3), 74.1 (2-CH), 78.2 (4-CH), 83.4 (5-CH), 171.5 (C = O) ppm. IR (film): $\tilde{\nu}$ = 1729, 1464, 1382, 1268, 1163, 1108, 1040 cm^{-1}. MS (EI): m/z = 287 [$M^+ - i$Pr] (14%), 187 (100), 113 (21), 103 (31), 75 (35). HRMS: calcd. for $C_{14}H_{27}O_4Si$ 287.1679, found 287.1669.

(2*R*,4*S*,5*R*)-(5-Methyl-4-(triisopropylsilyloxy)tetrahydrofuran-2-yl)-acetic Acid (20b): The silyl ether **20a** (1.50 g, 4.4 mmol) was added to a cooled solution of potassium hydroxide (2.04 g, 36.4 mmol) in methanol (18 mL). The resulting solution was stirred at ambient temperature overnight, and the bulk of the solvent evaporated. The residue was dissolved in water (20 mL) and the solution washed with diethyl ether (25 mL). This mixture was then acidified with ice-cold 2 M hydrochloric acid (16 mL) and extracted with chloroform (3 × 50 mL). The combined extracts were dried and the solvents evaporated to leave the *acid* **20b** (1.40 g, 97%) as a clear, colourless oil. $[\alpha]_D^{20} = +17.1$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03−1.05 (m, 21 H), 1.20 (d, J = 6.2 Hz, 3 H, 5-CH_3), 1.80 (ddd, J = 12.8, 9.6, 6.0 Hz, 1 H, 3-H_a), 2.02 (ddd, J = 12.8, 5.8, 2.3 Hz, 1 H, 3-H_b), 2.65 (d, J = 6.3 Hz, 2 H, 1′-CH_2), 3.91 (qd, J = 6.2, 2.9 Hz, 1 H, 5-H), 4.06 (ddd, J = 6.0, 2.9, 2.3 Hz, 1 H, 4-H), 4.48 (dtd, J = 9.6, 6.3, 5.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.5 (6 × CH_3), 18.5 (3 × CH), 20.4 (5-CH_3), 40.9 (3-CH_2), 41.7 (1-CH_2), 74.5 (2-CH), 78.6 (4-CH), 84.3 (5-CH), 176.0 (C = O) ppm. IR (film): $\tilde{\nu}$ = 3368, 1717, 1507, 1419, 1163, 1109, 1040 cm^{-1}. MS (EI): m/z = 316 [M^+] (11%), 273 [$M^+ - i$Pr] (24), 187 (100), 131 (58), 75 (64), HRMS: calcd. for $C_{13}H_{25}O_4Si$ 273.1522, found 273.1517. $C_{16}H_{32}O_4Si$: calcd. 60.76, H 10.13; found C 60.93, H 10.21.

(2*R*,4*S*,5*R*)-2-Aminomethyl-5-methyl-4-(triisopropylsilyloxy)-tetrahydrofuran (21): Triethylamine (0.06 mL, 0.41 mmol) was added to a solution of the acid **20b** (0.13 g, 0.41 mmol) in anhydrous toluene (8 mL), followed by diphenylphosphoranyl azide (0.088 mL, 0.41 mmol). The resulting solution was slowly warmed to 80 °C, and then stirred at this temperature for 2 h. The cooled solution was diluted with water (5 mL), stirred at ambient temperature for 16 h and extracted with chloroform (3 × 10 mL). The combined extracts were dried and the solvents evaporated to leave a brown oil, chromatography of which over silica gel (30% EtOAc in hexanes) gave the *amine* **21** (0.106 g, 90%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (m, 21 H), 1.27 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.73 (ddd, J = 13.1, 9.4, 6.2 Hz, 1 H, 3-H_a), 1.82 (ddd, J = 13.1, 6.1, 2.7 Hz, 1 H, 3-H_b), 3.18 (dd, J = 14.0, 6.1 Hz, 1 H, 2′-H_a), 3.49 (dd, J = 14.0, 6.4 Hz, 1 H, 2′-H_b), 3.66 (qd, J = 6.4, 3.1 Hz, 1 H, 5-H), 4.02 (ddd, J = 6.2, 6.1, 3.1 Hz, 1 H, 4-H), 4.16 (dddd, J = 9.4, 6.4, 6.1, 2.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.0 (5-CH_3), 17.9 (6 × CH_3), 19.8 (3 × CH), 38.0 (3-CH_2), 44.4 (CH_2NH_2), 76.5 (CH), 78.1 (CH), 83.9 (5-CH) ppm. IR (film): $\tilde{\nu}$ = 3430 cm^{-1}. MS (EI): m/z = 234 [$M^+ - i$Pr] (5%), 143 (100), 81 (93), 57 (70).

(2*RS*,4*SR*,5*RS*)-2-Chloromethyl-5-methyl-4-(triisopropylsilyloxy)-tetrahydrofuran (24): A sample of the racemic acid (±)-**20b** (0.10 g, 0.32 mmol) was dissolved in anhydrous benzene (5 mL) and the resulting solution stirred in an ice bath for 10 min before the addition of pyridine (1 drop) and *N*,*N*-dimethylformamide (1 drop). Oxalyl chloride (0.15 mL, 0.32 mmol) was then added dropwise and stirring continued for 3 h. The solvent was evaporated, the residue dissolved in anhydrous benzene (5 mL) and the solution once more evaporated to dryness. The crude acid chloride **22** was dissolved in anhydrous carbon tetrachloride (3 mL) and the resulting solution added dropwise to a stirred and refluxing suspension of sodium 2-mercaptopyridine *N*-oxide (57 mg, 0.38 mmol) in carbon tetrachloride (15 mL) containing 4-(dimethylamino)pyridine (3 mg). After 1.5 h at reflux, the suspension was cooled and filtered through Celite. The combined filtrate and washings were evaporated and the residue subjected to silica gel chromatography (5% EtOAc in petroleum ether) to give the racemic *chloride* **24** (72 mg, 73%) as a clear, colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05−1.07 (m, 21 H), 1.20 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.93−1.96 (m, 2 H, 3-CH_2), 3.59 (d, J = 4.8 Hz, 2 H, CH_2Cl), 3.95 (qd, J = 6.4, 3.1 Hz, 1 H, 5-H), 4.07 (ddd, J = 4.1, 3.6, 3.1 Hz, 1 H, 4-H), 4.39 (dtd, J = 6.2, 4.8, 2.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 12.0 (6 × CH_3), 17.9 (3 × CH), 20.5 (5-CH_3), 38.8 (3-CH_2), 47.2 (CH_2ClO), 77.3 (CH), 77.9 (CH), 83.5 (5-CH) ppm. IR (film): $\tilde{\nu}$ = 1402, 1371, 1249, 1106, 1058 cm^{-1}. MS (EI): m/z = 265 [M^+ (^{37}Cl)-iPr] (8%) 263 [M^+ (^{35}Cl)-iPr] (29), 187 (77), 131 (100), 97 (40), 75 (33). HRMS: calcd. for $C_{12}H_{24}{}^{35}ClO_2Si$ 263.1234, found 263.1225.

(2*RS*,4*SR*,5*RS*)-2-Chloromethyl-4-hydroxy-5-methyltetrahydrofuran (25a): Tetrabutylammonium fluoride (0.6 mL of a 1 M solution in tetrahydrofuran, 0.60 mmol) was added to a solution of the racemic chloride **24** (96 mg, 0.30 mmol) in anhydrous tetrahydrofuran (2 mL). The resulting solution was stirred for 40 h at ambient temperature; the solvent was then evaporated. The residue was separated by chromatography on silica gel (20% EtOAc in petroleum

ether) to give the racemic *chloro alcohol* **25a** (30 mg, 60%) as a clear, colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.2 Hz, 3 H, 5-CH_3), 2.03−2.08 (m, 2 H, 3-CH_2), 3.59 (d, *J* = 5.0 Hz, 2 H, CH_2Cl), 4.02−4.05 (m, 2 H, 4-and 5-H), 4.39 (tdd, *J* = 5.0, 2.8, 2.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 19.5 (5-CH_3), 38.1 (3-CH_2), 47.0 (CH_2Cl), 77.2 (CH), 77.3 (CH), 82.9 (5-CH) ppm. IR (film): $\tilde{\nu}$ = 3430, 1645, 1444, 1350 cm^{-1}. MS (EI): *m*/*z* = 115 [M$^+$ − Cl] (17%), 101 (71), 71 (53), 70 (32), 57 (100). HRMS: calcd. for $C_6H_{11}O_2$ 115.0759; found 115.0757.

(2*R*,4*S*,5*R*)-2-Iodomethyl-5-methyl-4-(triisopropylsilyloxy)-tetrahydrofuran (25b): The acid (+)-**20b** (82 mg, 0.26 mmol) was dissolved in anhydrous benzene (3 mL) containing pyridine (1 drop) and *N*,*N*-dimethylformamide (1 drop). The resulting stirred solution was cooled to 0 °C and treated dropwise with oxalyl chloride (0.12 mL, 0.26 mmol). After 3 h at 0 °C, the solvent was evaporated, the residue dissolved in anhydrous benzene (5 mL) and the solution evaporated. The residue was dissolved in anhydrous cyclohexene (4 mL) and the solution added to refluxing cyclohexene (10 mL) containing iodoform (112 mg, 0.28 mmol), 2-mercaptopyridine *N*-oxide sodium salt (44 mg, 0.28 mmol), and 4-(dimethylamino)pyridine (3 mg). After 15 h at reflux, the resulting suspension was cooled and filtered through Celite. The filtrate and washings were combined and the solvents evaporated. Chromatography of the residue on silica gel (5% EtOAc in petroleum ether) gave the *iodide* **25b** (54 mg, 60%) as a clear colourless oil. $[\alpha]_D^{18}$ = +24.6 (*c* = 8.7, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00−1.02 (m, 21 H), 1.25 (d, *J* = 6.3 Hz, 3 H, 5-CH_3), 1.74 (ddd, *J* = 12.7, 6.5, 2.9 Hz, 1 H, 3-H_a), 1.93 (ddd, *J* = 12.7, 6.0, 2.9 Hz, 1 H, 3-H_b), 3.22 (d, *J* = 4.8 Hz, 2 H, CH_2I), 3.92 (qd, *J* = 6.3, 3.2 Hz, 1 H, 5-H), 4.02 (ddd, *J* = 6.0, 3.2, 2.9 Hz, 1 H, 4-H), 4.39 (dtd, *J* = 6.5, 4.8, 2.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 11.0 (CH_2I), 12.0 (6 × CH_3), 17.9 (3 × CH), 19.9 (5-CH_3), 41.8 (3-CH_2), 77.0 (CH), 78.1 (CH), 83.9 (5-CH) ppm. IR (film): $\tilde{\nu}$ = 1445, 1250, 1156, 1071 cm^{-1}. MS (EI): *m*/*z* = 355 [M$^+$ − *i*Pr] (3%), 187 (100), 141 (35), 127 (40), 75 (15). HRMS: calcd. for $C_{12}H_{24}IO_2Si$ 355.0590, found 355.0582.

(2*R*,4*S*,5*R*)-4-Hydroxy-2-iodomethyl-5-methyltetrahydrofuran (25c): A solution of the iodide **25b** (64 mg, 0.20 mmol) in tetrahydrofuran (1 mL) was stirred with tetrabutylammonium fluoride (0.4 mL of a 1 M solution in tetrahydrofuran, 0.40 mmol) at ambient temperature for 40 h. The solvent was evaporated and the residue chromatographed on silica gel (20% EtOAc in petroleum ether) to give the *iodo alcohol* **25c** (23 mg, 69%) as a clear, colourless oil. $[\alpha]_D^{18}$ = +20.5 (*c* = 2.0, $CHCl_3$) [ref.[16] $[\alpha]_D$ = −26.5 (*c* = 1.8, $CHCl_3$)]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.4 Hz, 3 H, 5-CH_3), 1.91 (ddd, *J* = 13.3, 8.6, 6.2 Hz, 1 H, 3-H_a), 2.05 (ddd, *J* = 13.3, 6.2, 3.0 Hz, 1 H, 3-H_b), 3.34 (dd, *J* = 10.2, 6.2 Hz, 1 H, C$H_a$$H_b$I), 3.41 (dd, *J* = 10.2, 4.9 Hz, 1 H, C$H_a$$H_b$I), 3.97 (qd, *J* = 6.4, 3.2 Hz, 1 H, 5-H), 4.05 (ddd, *J* = 8.6, 6.2, 3.2 Hz, 1 H, 4-H), 4.16 (tdd, *J* = 6.2, 4.9, 3.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 10.4 (CH_2I), 19.8 (5-CH_3) 41.1 (3-CH_2), 77.2 (CH), 77.6 (CH), 83.3 (5-CH) ppm. MS (EI): *m*/*z* = 242 [M$^+$] (2%), 115 (31), 101 (100), 71 (70).

(−)-Muscarine Iodide (25d): Trimethylamine (0.05 mL) was added to a solution of the iodo alcohol **25c** (10 mg) in ethanol (0.2 mL), the resulting solution heated at 70 °C for 4 h in a sealed tube, and then allowed to cool slowly overnight. The solvent was evaporated to leave a solid residue which was crystallised from acetone to give a pure sample of (−)-muscarine iodide (**25d**) as an unstable colourless solid, m.p. 135−137 °C [ref.[16] m.p. 138−142 °C].

(3*R*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-1-phenyl-1-pentyn-3-ol (31a): *n*BuLi (5.24 mL of a 2.5 M solution in hexanes, 13 mmol) was added to anhydrous tetrahydrofuran (50 mL) and the stirred solution cooled to −78 °C. 12-Crown-4 (2.29 g, 13 mmol) was added followed by the dropwise addition of a solution of phenylacetylene (1.34 g, 13 mmol) in tetrahydrofuran (2 mL). After 20 min at −78 °C, a solution of the (*S*)-aldehyde **30**[43] (3.00 g, 9.62 mmol) in tetrahydrofuran (10 mL) was slowly added, the resulting solution slowly warmed to ambient temperature over 4 h, and then quenched by the addition of saturated aqueous ammonium chloride (50 mL). The resulting mixture was extracted with diethyl ether (3 × 50 mL), the combined extracts dried, and the solvents evaporated. Chromatography of the residue (10% Et_2O in petroleum ether) gave the (3*R*,4*S*)-*alkynol* **31a**. $[\alpha]_D^{20}$ = −9.1 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 9 H, *t*Bu), 1.11 (d, *J* = 6.2 Hz, 3 H, 5-CH_3), 2.55 (d, *J* = 6.1 Hz, 1 H, OH), 3.99 (qd, *J* = 6.2, 3.5 Hz, 1 H, 4-H), 4.41 (dd, *J* = 6.1, 3.5 Hz, 1 H, 3-H), 7.17−7.21 (m, 3 H), 7.28−7.33 (m, 8 H), 7.62−7.65 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.8 (5-CH_3), 19.5 (CSi), 27.4 (3 × CH_3), 68.4 (2-C), 69.8 (3-CH), 72.9 (4-CH), 87.7 (1-C), 123.3 (C), 128.6 (2 × CH), 130.4 (CH), 132.1 (2 × CH), 136.3 (CH), 136.4 (2 × CH), 136.6 (2 × C), 136.6 (2 × C) ppm. IR (film): $\tilde{\nu}$ = 3308 (br.), 3070, 2857, 2361, 1619, 1443, 1259, 1112, 822 cm^{-1}. MS (APcI): *m*/*z* = 415 [M$^+$ + H] (50%), 397 [M$^+$ − H_2O] (100%). HRMS calcd. for $C_{27}H_{31}O_2Si$ 415.2093, found 415.20946.

Approximately 11% of the (3*S*,4*S*)-isomer was present in the sample, as determined by resonances in the ^{1}H NMR spectrum at δ_H = 3.94 (4-H) and 4.33 (3-H) ppm.

(2*S*,3*R*)-5-Phenyl-4-pentyne-2,3-diol (31b): Tetrabutylammonium fluoride (TBAF; 16.4 mL of a 1 M solution in tetrahydrofuran, 16.4 mmol) was added to a stirred solution of the alkynol **31a** (3.40 g, 8.21 mmol) in tetrahydrofuran (100 mL). The resulting solution was stirred for 2 h at ambient temperature, diluted with dichloromethane (150 mL) and washed with brine (60 mL). The resulting organic solution was dried and the solvents evaporated to leave a brown oil which was purified by column chromatography (EtOAc/petroleum ether, 1:1) to give the *alkynediol* **31b** (1.34 g, 93%) as a colourless solid, m.p. 65−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 2.00 (d, *J* = 6.7 Hz, 1 H, OH), 2.44 (d, *J* = 6.7 Hz, 1 H, OH), 3.92 (app. quintd, *J* ≈ 6.4, 3.7 Hz, 1 H, 2-H), 4.47 (dd, *J* = 6.7, 3.7 Hz, 1 H, 3-H), 7.08−7.12 (m, 3 H), 7.24−7.27 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.1 (1-CH_3), 68.0 (3-CH), 70.8 (2-CH), 86.5 (4-C), 86.9 (5-C), 122.5 (C), 128.7 (2 × CH), 129.1 (CH), 132.2 (2 × CH) ppm. IR (nujol): $\tilde{\nu}$ = 3243 (br.), 2348, 1489, 1426, 1084, 996, 914, 755, 689 cm^{-1}. MS (ApcI): *m*/*z* = 159 [M$^+$ + H − H_2O] (100%). The minor (2*S*,3*S*)-isomer (ca. 12%) was evident from the ^{1}H NMR spectrum: δ_H = 2.38 (OH), 3.88 (2-H), and 4.27 (3-H).

(2*S*,3*S*,4*R*,5*R*)-4-Iodo-2-methyl-5-phenyltetrahydro-3-furanol (33): A stirred solution of the alkyne diol **31b** (2.11 g, 12 mmol) in hexane (60 mL) containing methanol (1 mL), quinoline (0.5 mL) and 5% palladium on calcium carbonate (300 mg) was stirred under one atmosphere of hydrogen for 2 h, by which time 270 mL of gas had been absorbed. The mixture was filtered through Celite and the solid washed with dichloromethane. Evaporation of the combined filtrates gave (2*S*,3*R*,4*Z*)-5-phenyl-4-pentene-2,3-diol (**32**) contaminated with quinoline which was immediately used in the following iodocyclisation without further purification. **32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 3.84 (qd, *J* = 6.4, 3.6 Hz, 1 H, 2-H), 4.45 (dd, *J* = 9.5, 3.6 Hz, 1 H, 3-H), 5.69 (dd, *J* = 11.7, 9.5 Hz, 1 H, 4-H), 6.56 (d, *J* = 11.7 Hz, 1 H, 5-H), 7.13−7.20 (m, 3 H), 7.21−7.23 (m, 2 H) ppm. ^{13}C NMR

(100.6 MHz, $CDCl_3$): δ = 19.5 (1-CH_3), 74.5 (3-CH), 75.6 (2-CH), 129.0 (CH), 129.3 (2 × CH), 130.1 (2 × CH), 134.0 (4-CH), 136.9 (5-CH), 142.5 (C) ppm. MS (APcI): *m*/*z* = 179 [M^+ + H] (20%), 160 [$M^+ - H_2O$] (100%). A proton resonance at δ = 5.55 (4-H) was used to show the expected presence of ca. 11% of the (3*S*)-isomer.

The crude (*Z*)-alkenediol **32** (ca. 12 mmol) was dissolved in anhydrous acetonitrile (40 mL) maintained at 0 °C. Sodium hydrogen carbonate (3.02 g, 36 mmol) was then added and the resulting suspension stirred for 5 min before the addition of solid iodine (9.13 g, 36 mmol) in one portion. After 4 h at 0 °C, the mixture was decolourised by the addition of saturated aqueous sodium thiosulfate (40 mL) and extracted with diethyl ether (2 × 80 mL). The combined extracts were washed with 1 M hydrochloric acid (90 mL) and water (40 mL), dried, and the solvents evaporated. The brown oily residue was separated by chromatography (10% EtOAc in petroleum ether) to give the *iodotetrahydrofuran* **33** (1.86 g, 51% for the two steps) as a light-sensitive orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 6.5 Hz, 3 H, 2-CH_3), 3.22 (br. s, 1 H, 3-OH), 3.88 (qd, *J* = 6.5, 2.8 Hz, 1 H, 2-H), 4.27 (dd, *J* = 4.4, 2.8 Hz, 1 H, 4-H), 4.46 (m, 1 H, 3-H), 4.56 (d, *J* = 4.4 Hz, 1 H, 5-H), 7.17−7.24 (m, 3 H), 7.33−7.37 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.9 (2-CH_3), 39.2 (4-CH), 79.6 (5-CH), 80.8 (2-CH), 84.5 (3-CH), 124.5 (CH), 126.3 (2 × CH), 126.5 (2 × CH), 139.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3391 cm^{-1}. MS (APcI): *m*/*z* = 305 [M^+ + H] (100%).

(2*S*,3*S*,5*S*)-2-Methyl-5-phenyltetrahydro-3-furanol (34a): The iodotetrahydrofuran **33** (0.44 g, 1.46 mmol) and 10% palladium on carbon (130 mg) were stirred in ethyl acetate (10 mL) containing triethylamine (0.40 mL, 2.89 mmol) under an atmosphere of hydrogen for 16 h, by which time 32.7 mL of gas had been absorbed. The resulting suspension was filtered through a mixture of Celite and silica and the solid washed with ethyl acetate. Evaporation of the combined filtrates left the *tetrahydrofuranol* **34a** (0.26 g, 98%) as a colourless solid, m.p. 80−81 °C. $[\alpha]_D^{20}$ = −62.0 (*c* = 2.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 1.65 (d, *J* = 3.8 Hz, 1 H, 3-OH), 1.84 (ddd, *J* = 13.3, 10.0, 3.1 Hz, 1 H, 4-H_a), 2.02 (ddd, *J* = 13.3, 5.8, 2.2 Hz, 1 H, 4-H_b), 3.85 (qd, *J* = 6.4, 2.9 Hz, 1 H, 2-H), 3.93 (app. br. d, *J* = ca. 3.0 Hz, 1 H, 3-H), 4.94 (dd, *J* = 10.0, 5.8 Hz, 1 H, 5-H), 7.04−7.09 (m, 1 H), 7.12−7.15 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.3 (2-CH_3), 44.1 (4-CH_2), 78.4 (3-CH), 80.2 (5-CH), 83.6 (2-CH), 126.3 (2 × CH), 127.9 (CH), 128.8 (2 × CH), 142.5 (C) p.p.m. IR (nujol): $\tilde{\nu}$ = 3363, 1488, 1452, 1356, 1323 cm^{-1}. HRMS: calcd. for $C_{11}H_{15}O_2$ [M^+ + H] 179.1072, found 179.1071. $C_{11}H_{14}O_2$: calcd. C 74.12, H 7.92; found C 74.07, 7.73.

(2*S*,3*R*,5*S*)-3-Acetyloxy-2-methyl-5-phenyltetrahydrofuran (34b): Acetic anhydride (0.14 mL, 1.53 mmol) was added to a stirred solution of the tetrahydrofuranol **34a** (0.31 g, 1.40 mmol) in anhydrous pyridine (1 mL). The resulting solution was stirred at ambient temperature overnight, diluted with diethyl ether (20 mL), washed with 2 M aqueous copper(II) sulfate (20 mL) and brine (20 mL), dried, and the solvents evaporated to leave the *acetate* **34b** (0.30 g, 97%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.5 Hz, 3 H, 2-CH_3), 1.86−2.01 (m, 1 H, 4-H_a), 2.05 (s, 3 H), 2.21 (app. dd, *J* = 13.7, 5.3 Hz, 1 H, 4-H_b), 4.07 (qd, *J* = 6.5, 2.3 Hz, 1 H, 2-H), 4.91 (app. br. d, *J* = ca. 6.0 Hz, 3-H), 4.99 (dd, *J* = 10.6, 5.3 Hz, 1 H, 5-H), 7.19−7.22 (m, 1 H), 7.26−7.29 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.9 (2-CH_3), 20.2 (CH_3), 39.7 (4-CH_2), 78.7 (3-CH), 80.0 (2-CH), 82.1 (5-CH), 124.9 (2 × CH), 126.7 (CH), 127.4 (2 × CH), 140.2 (C), 169.9 (C = O) ppm. IR (film): $\tilde{\nu}$ = 1724, 1444, 1377, 999, 912 cm^{-1}. MS (APcI): *m*/*z* = 221 [M^+ + H] (80%), 161 (100). HRMS: calcd. for $C_{13}H_{17}O_3$ 221.1178, found 221.1181.

(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldiphenylsilyloxy)hex-2-yn-4-ol (37): *n*BuLi (5.3 mL of a 2.5 solution in hexanes, 13 mmol) was added to anhydrous tetrahydrofuran (50 mL), stirred and maintained at −78 °C. 12-Crown-4 (2.29 g, 13 mmol) was then added followed by the dropwise addition of a solution of *O*-*tert*-butyldiphenylsilylpropargyl alcohol (3.89 g, 13 mmol) in tetrahydrofuran (2 mL). After 20 min at −78 °C, the (*S*)-*O*-silyllactaldehyde **36**[43] (1.80 g, 9.56 mmol) was added and the resulting solution slowly warmed to ambient temperature over 4 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined extracts were dried and the solvents evaporated to leave a yellow oil which was purified by chromatography (10% EtOAc in petroleum ether) to give the *alkynol* **37** (2.98 g, 65%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.81 (s, 9 H), 0.97 (s, 9 H), 1.10 (d, *J* = 6.2 Hz, 3 H, 6-CH_3), 2.21 (d, *J* = 5.0 Hz, 1 H, OH), 3.77 (qd, *J* = 6.2, 3.9 Hz, 1 H, 5-H), 4.16 (br. signal, 1 H, 4-H), 4.28 (d, *J* = 1.4 Hz, 2 H, 1-CH_2), 7.33−7.35 (m, 6 H), 7.61−7.64 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −1.0 (2 × CH_3), 18.5 (6-CH_3), 19.6 (C), 20.3 (C), 26.2 (3 × CH_3), 27.0 (3 × CH_3), 53.1 (1-CH_2), 67.4 (5-CH), 71.4 (4-CH), 83.3 (3-C), 84.8 (2-C), 128.1 (4 × CH), 130.2 (2 × CH), 135.2 (2 × C), 136.0 (4 × CH) ppm. IR (film): $\tilde{\nu}_{max}$ = 3444, 2360, 1472, 1428, 1255, 1112, 1007 cm^{-1}. MS (APcI): *m*/*z* = 483 [M^+ + H] (50%), 465 [$M^+ + H - H_2O$] (100). HRMS (NH_4CI): calcd. for $C_{28}H_{46}NO_3Si$ 500.3016 ($M^+ + NH_4$), found 500.3012. The minor (4*S*,5*S*)-isomer (ca. 9%) was visible at δ_H = 3.70 (5-H) and 3.96 (4-H).

(4*R*,5*S*,2*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldiphenylsilyloxy)hex-2-en-4-ol (38): The alkynol **37** (1.22 g, 2.52 mmol) and quinoline (0.09 mL, 0.76 mmol) were stirred in methanol (10 mL) containing 5% palladium on calcium carbonate (0.05 g) under hydrogen until ca. 56 mL (2.52 mmol) had been absorbed (0.25 h). The resulting suspension was filtered through Celite and the solid washed with diethyl ether. The combined filtrates were washed with 1 M hydrochloric acid (40 mL) and brine (40 mL), dried, and the solvents evaporated to give the (*Z*)-*alkene* **38** (1.09 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.04 (s, 3 H), −0.03 (s, 3 H), 0.85 (s, 9 H), 1.01 (d, *J* = 6.2 Hz, 3 H, 6-CH_3), 1.05 (s, 9 H), 3.67 (qd, *J* = 6.2, 3.8 Hz, 1 H, 5-H), 4.08 (br. dd, *J* = 8.2, 3.8 Hz, 4-H), 4.21 (dd, *J* = 13.3, 5.4 Hz, 1 H, 1-H_a), 4.32 (dd, *J* = 13.3, 6.8 Hz, 1 H, 1-H_b), 5.44 (dd, *J* = 8.3, 8.2 Hz, 1 H, 3-H), 5.79 (ddd, *J* = 8.3, 6.8, 5.4 Hz, 1 H, 2-H), 7.36−7.45 (m, 6 H), 7.71−7.74 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −1.0 (2 × CH_3), 15.7 (6-CH_3), 18.4 (C), 19.5 (C), 26.2 (3 × CH_3), 27.0 (3 × CH_3), 61.0 (1-CH_2), 71.6 (5-CH), 72.1 (4-CH), 128.0 (4 × CH), 130.1 (2 × CH), 132.6 (2-CH), 135.1 (2 × C), 135.1 (2 × C), 135.2 (3-CH), 136.0 (4 × CH) ppm. IR (film): $\tilde{\nu}$ = 3444, 1590, 1472, 1428, 1255, 1112 cm^{-1}. MS (APcI): *m*/*z* = 485 [M^+ + H] (10%), 467 [$M^+ + H - H_2O$] (100). HRMS: calcd. for $C_{28}H_{45}O_3Si_2$ 485.2907, found 485.2904. $C_{28}H_{44}O_3Si_2$: calcd. C 69.37, H, 9.15; found C 68.94, H 9.12.

(2*R*,3*R*,4*S*,5*S*)-2-*O*-(*tert*-Butyldiphenylsilylmethyl)-3-iodo-5-methyltetrahydrofuran-4-ol (39): Sodium hydrogen carbonate (0.46 g, 5.45 mmol) was added to a stirred solution of the (*Z*)-alkene **38** (0.88 g, 1.8 mmol) in anhydrous acetonitrile (40 mL) maintained at −10 °C. After 5 min, iodine monobromide (0.75 g, 3.63 mmol) was added in one portion and stirring continued at −10 °C for 3.5 h (TLC monitoring). Saturated aqueous sodium thiosulfate (20 mL) and dichloromethane (40 mL) were added and the resulting layers

separated. The aqueous layer was extracted with dichloromethane (40 mL), the combined organic solutions washed with brine (40 mL), dried, and the solvents evaporated. Chromatography (10% EtOAc in petroleum ether) of the residue gave the *iodotetrahydrofuran* **39** (0.45 g, 68%) as a pale yellow oil. $[\alpha]_D^{20} = +18.2$ (c = 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9 H), 1.34 (d, J = 6.6 Hz, 3 H, 5-CH_3), 1.55 (app. br. s, 1 H, OH), 3.65 (dd, J = 10.5, 5.8 Hz, 1 H, 1′-H_a), 3.69−3.73 (m, 1 H, 2-H), 3.70 (qd, J = 6.6, 3.6 Hz, 5-H), 3.82 (dd, J = 10.5, 4.3 Hz, 1 H, 1′-H_b), 4.19 (dd, J = 4.3, 3.6 Hz, 1 H, 3-H), 4.34 (app. br. t, J ca. 3.9 Hz, 1 H, 4-H), 7.27−7.38 (m, 6 H), 7.60−7.68 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.7 (5-CH_3), 20.5 (C), 27.3 (3 × CH_3), 36.0 (3-CH), 68.3 (1′-CH_2), 77.8 (4-CH), 79.4 (5-CH), 82.1 (2-CH), 128.1 (4 × CH), 130.2 (2 × CH), 134.7 (2 × C), 136.1 (4 × CH) ppm. IR (film): $\tilde{\nu}$ = 3425, 1471, 1428, 1261 cm^{-1}. MS (APcI): m/z = 419 (M^+ − Ph, 40%), 291 (M^+ − Ph-HI, 100%). HRMS (NH_4CI): calcd. for $C_{22}H_{33}INO_3Si$ 514.1274 [M + NH_4^+], found 514.1271. $C_{22}H_{29}IO_3Si$: calcd. C 53.23, H 5.89; found C 53.08, H 6.12.

(2*S*,4*R*,5*S*)-2-*O*-(*tert*-Butyldiphenylsilylmethyl)-5-methyltetrahydrofuran-4-ol (40a): The iodotetrahydrofuran **39** (0.45 g, 1.22 mmol), triethylamine (0.34 mL, 2.44 mmol), and 10% palladium on carbon (0.11 g) were stirred in ethyl acetate (10 mL) at ambient temperature under an atmosphere of hydrogen for 16 h. The resulting slurry was filtered through Celite and the solid washed with ethyl acetate. The combined filtrate and washings were diluted with diethyl ether (20 mL), the solution washed with 1 M hydrochloric acid (40 mL) and brine (20 mL), dried, and the solvents evaporated to give the *tetrahydrofuran* **40a** (0.33 g, 91%) as a colourless oil. $[\alpha]_D^{20} = +4.3$ (c = 1.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 9 H), 1.15 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.81 (ddd, J = 10.2, 6.7, 3.5 Hz, 1 H, 3-H_a), 2.04−2.12 (m, 1 H, 3-H_b), 3.59 (dd, J = 10.8, 6.7 Hz, 1′-H_a), 3.64 (dd, J = 10.8, 4.2 Hz, 1 H, 1′-H_b), 3.83 (qd, J = 6.4, 3.6 Hz, 1 H, 5-H), 3.94 (app. br. td, J = 6.7, 3.6 Hz, 1 H, 4-H), 4.15−4.21 (m, 1 H, 2-H), 7.29−7.37 (m, 6 H), 7.60−7.66 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.0 (C), 18.2 (5-CH_3), 25.8 (3 × CH_3), 35.4 (3-CH_2), 65.0 (1′-CH_2), 75.7 (4-CH), 76.5 (2-CH), 81.3 (5-CH), 126.7 (4 × CH), 128.6 (2 × CH), 133.8 (2 × C), 134.6 (4 × CH) ppm. IR (film): $\tilde{\nu}$ = 3397, 1472, 1428, 1390, 1260, 1111 cm^{-1}. MS (APcI): 293 (M^+ − Ph, 100%). HRMS (NH_4CI): calcd. for $C_{22}H_{34}NO_3Si$ 388.2308 (M + NH_4^+), found 388.2312.

(2*S*,4*R*,5*S*)-(4-Hydroxy-5-methyltetrahydrofuran-2-yl)methanol (40b): Ammonium fluoride (0.27 g, 7.17 mmol) was added to a solution of the tetrahydrofuran **40a** (0.29 g, 1.19 mmol) in methanol (5 mL), the resulting solution stirred at ambient temperature for 16 h, and then evaporated. The resulting brown solid was separated by column chromatography (10% MeOH in CH_2Cl_2) to give the *diol* **40b** (0.09 g, 56%) as a colourless oil. $[\alpha]_D^{20} = -5.8$ (c = 0.2, $CHCl_3$), (ref.[19] $[\alpha]_D^{20} = -6.0$ (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.4 Hz, 3 H, 5-CH_3), 1.54 (br. s, 2 H, 2 × OH), 1.76 (ddd, J = 13.2, 6.5, 3.5 Hz, 1 H, 3-H_a), 1.96 (ddd, J = 13.2, 9.1, 6.4 Hz, 3-H_b), 3.43 (dd, J = 11.9, 4.9 Hz, 1 H, 1′-H_a), 3.70 (dd, J = 11.9, 3.0 Hz, 1 H, 1′-H_b), 3.85 (qd, J = 6.4, 3.5 Hz, 1 H, 5-H), 3.93 (m, 1 H, 4-H), 4.17−4.21 (m, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.9 (5-CH_3), 35.1 (3-CH_2), 63.7 (1′-CH_2), 76.6 (4-CH), 77.7 (2-CH), 81.8 (5-CH) ppm. HRMS: calcd. for $C_6H_{13}O_3$ [M^+ + H] 133.0865, found 133.0864. These data correspond to those previously reported.[19]

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