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# Synthesis of (*E*)-4-methylhexa-3,5-dien-1-ol and its Diels–Alder reaction with thioester dienophiles: a short enantioselective synthesis of bicyclic lactones

Leonidas-Dimitrios Syntrivanis[a] and Jeremy Robertson*[a]

**Abstract:** The preparation of (*E*)-4-methylhexa-3,5-dien-1-ol has been achieved in a single step from 3-methylpenta-1,4-diene via deprotonation with BuLi, alkylation with paraformaldehyde, and metal counterion exchange in situ to promote oxy-anion accelerated [1,3]-sigmatropic shift. This alcohol is shown to undergo intermolecular Diels–Alder reaction with 3-isopropyl acrylate thioesters; the so-formed exclusive *endo*-adduct may then be closed to the bicyclic lactone, the product of formal intramolecular Diels–Alder reaction (a much more difficult process). Use of chiral thioesters results in an enantioselective synthesis of this bicyclic lactone, an intermediate with application to eunicellane (cladiellane) diterpene synthesis.

## Introduction

For the synthesis of stereodefined multi-substituted cyclohexenes, few strategies compare favourably with those based on the Diels–Alder (DA) reaction and, especially, its intramolecular (IMDA) variant. [1] Linking the component diene and dienophile in an intramolecular cycloaddition improves control of regio- and stereochemistry and, in some cases, results in an increase in rate in comparison with the equivalent intermolecular reaction. If the linkage is cleavable, for example by incorporating an ester, acetal, or silyl group, the products of overall intermolecular DA reactions may be accessed with the selectivity and rate benefits of the intramolecular reaction.

In this context, lactones of general structure **1** (Figure 1), valuable intermediates in the synthesis of eleutherobin and related diterpenes of the eunicellane (cladiellane) class, [2] are available using IMDA cycloadditions of appropriately-substituted hexa-1,3-dienyl acrylates **2**. [3] This general approach suffers from the significant steric and electronic deactivation of the dienophile imparted by the 3-isopropyl substituent and, in the lower energy s-*cis* ester conformation, the diene and dienophile components are not well disposed to interact. Thus, thermal IMDA cycloadditions of this type often require a reaction temperature in excess of 200 °C, extended reaction times, and return merely moderate yields and diastereoselectivities. [2c-e], [3b-e] Taguchi introduced TfN[Al(Me)Cl]$_2$ as a bidentate Lewis acid to promote the formation and activation of the s-*trans* ester conformation; inclusion of this additive (1.1 equiv.) allows the IMDA to proceed at 80 °C, the reactions typically being complete in a few hours. [3g,h]

Full control of the lactone absolute stereochemistry may be achieved by asymmetric induction from the R-substituent in IMDA precursor **2**; [3d] however, for eleutherobin, this requires a subsequent inversion at the R-bearing centre. Where no R-group is present (**2**, R = H), an alternative approach is required and we report herein proof-of-principle results concerning a potential solution.

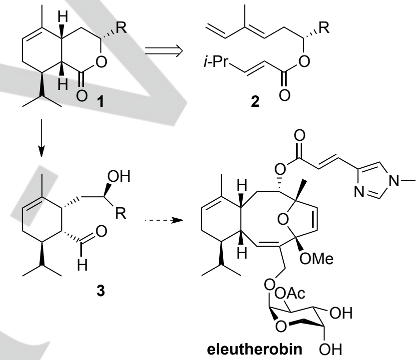

Figure 1. Bicyclic lactones **1**, accessible by IMDA reaction, may be elaborated into precursors **3** en route to eleutherobin and related diterpenes.

## Results and Discussion

The parent alcohol **4** (Scheme 1), required for lactone **1** (R = H), is currently available as a mixture of geometrical isomers from β-ocimene **5** by ozonolysis and reduction, [4] or in four steps from acetyl cyclopropane **6**. [5] The *E*-isomer may be prepared from tiglic aldehyde **7** via HWE reaction, alkene deconjugation, and ester reduction. [6] The *Z*- isomer has been prepared from hex-5-en-3-yn-1-ol **8** by intramolecular carbometalation and protonation. [7] Experience within our group with the addition of lithiated 3-methylpenta-1,4-diene to aldehydes suggested the enticing possibility of a shorter stereoselective route to this alcohol. [8] As expected, [9] addition of 3-methylpentadienyl lithium to a suspension of paraformaldehyde in THF provided an equimolar mixture of the desired alcohol **4**, exclusively as the *E*-isomer, and the branched isomer **10**. Although the two isomers are readily separable by column chromatography, the crude mixture of alcohols could be treated with KH and 18-crown-6 in THF to yield the desired linear dienyl alcohol exclusively by oxy-anion-accelerated [1,3]-shift. [10]

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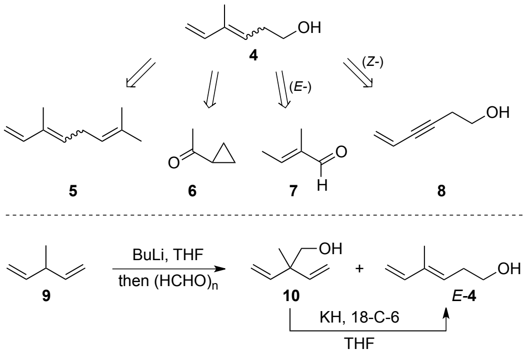


Scheme 1. Syntheses of 4-methylhexa-3,5-dien-1-ol **4**.

The two-step sequence comprising organometallic addition then deprotonation with KH is effectively always employed for the production then [1,3]- or [3,3]-sigmatropic rearrangement of allylic alcohols. This is somewhat cumbersome but direct rearrangement of the lithium alkoxide could not be achieved, even with 12-crown-4 added to the reaction mixture and prolonged heating. However, it seemed plausible, despite scant literature precedent,[11] that addition of a THF-soluble potassium salt to the mixture of lithium alkoxides (**11** and **12**, Figure 2) might effect cation exchange to promote rapid [1,3]-shift from the branched potassium alkoxide **13**. In practice, addition of 1.0 equiv. each of 18-crown-6 and a THF solution of *t*-BuOK completed the rearrangement within minutes. Under these strongly basic conditions, small amounts of diene isomer **15**[12] were also formed (Table 1, entry 1). This side reaction could not be entirely eliminated without compromising the conversion of the branched to linear dienyl alcohol isomers (entries 2, 3). Use of solid *t*-BuOK gave a complex mixture, while KHMDS (THF solution) led to inferior results (entries 4, 5). Addition of paraformaldehyde to 3-methylpentadienyl potassium[13] provided an ~75 : 25 ratio of alcohols **4** and **10**, respectively, but, again, isomer **15** was generated following addition of 18-crown-6 to the reaction mixture (entry 6).

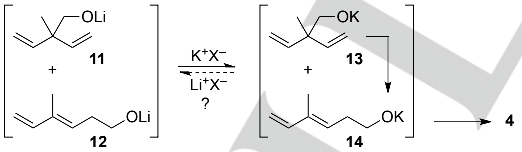
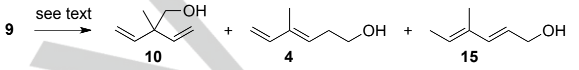


Figure 2. Proposed metal counterion exchange and oxy-anion accelerated [1,3]-shift in situ.

Further potassium and cesium salts were assayed, as it was envisaged that less basic anions would effect isomerisation into alcohol **15** to a lesser extent. Among these, $K_2CO_3$, KF, and $KPF_6$ failed to promote the desired reaction, probably owing to their low solubility in THF (entries 7–9). Use of CsF in a THF/DMF solvent mixture gave no improvement, while $KPF_6$ in a THF/DME mixture afforded an improved **4** : **10** ratio but generated unidentified side products, possibly as a result of the long reaction time required (entries 10, 11).

Finally, it was found that potassium trimethylsilanolate (KOTMS) was an effective alternative to *t*-BuOK that promoted the formation of diene isomer **15** only very slowly, allowing clean production of dienyl alcohol **4** (entry 12). Use of sub-stoichiometric quantities of KOTMS gave only partial conversion (entry 13). In the optimised procedure, 1.0 equiv. of 18-crown-6 and 2.0 equiv. of KOTMS are added to the lithium alkoxide mixture, and the reaction is quenched with brine after 15 minutes to provide diene **4** containing traces (<5%) of internal diene **15**, in 55% yield after bulb-to-bulb distillation.

Table 1. The effect of additives on the production of branched (**10**), linear (**4**), and isomerised (**15**) alcohols.



| Entry | Additive (equiv.)[a][b] | Time[c] | Ratio[d] **10** : **4** : **15** |
|---|---|---|---|
| 1 | *t*-BuOK (1.0) | 5 min | trace : 83 : 17 |
| 2 | *t*-BuOK (0.8) | 5 min | 21 : 72 : 7 |
| 3 | *t*-BuOK (0.5) | 20 min | 50 : 50 : 0 |
| 4 | *t*-BuOK (1.0)[e] | 12 h | complex |
| 5 | KHMDS (1.0) | 30 min | 21 : 72 : 7 |
| 6 | None[f] | 30 min | 8 : 77 : 15 |
| 7 | $K_2CO_3$ (1.0)[e] | 12 h | 50 : 50 : 0 |
| 8 | KF (1.0)[e] | 12 h | 50 : 50 : 0 |
| 9 | $KPF_6$ (1.0)[e] | 12 h | 50 : 50 : 0 |
| 10 | $KPF_6$ (1.0)[g] | 12 h | 9 : 91 : 0 |
| 11 | CsF (1.0)[h] | 12 h | 19 : 62 : 19 |
| 12 | KOTMS (2.0) | 15 min | trace : 100 : trace |
| 13 | KOTMS (0.5) | 12 h | 44 : 56 : 0 |

[a] Added at RT after the 2-methylpentadienyl lithium had been consumed as evidenced by disappearance of the red colouration of the organometallic and after the addition of 18-crown-6; this stage of the reaction was always performed in THF; [b] added as a solution in THF except where specified; [c] refers to the period following the addition of the additive up to the point at which the reaction is quenched with brine; [d] determined by integration of peaks in the $^1$H NMR spectrum of the crude product mixture; [e] added as a solid; [f] 2-methylpentadienyl lithium/potassium generated using Schlosser's method;[13] [g] added as a solution in THF/DME, 3 : 1; [h] added as a solution in THF/DMF, 3 : 1.

The requirement for a stoichiometric quantity of added KOTMS or *t*-BuOK is consistent with an effectively irreversible counterion exchange from both lithium alkoxides **11** and **12** to the corresponding potassium alkoxides **13** and **14**. Assuming that alkoxide **13** rearranges rapidly to **14**, it would appear that **14** is stable under the reaction conditions and that the reaction **14** +

ROLi → **12** + ROK does not proceed at an appreciable rate. This is interesting given that both *t*-BuOK and KOTMS *do* effect exchange with **11** and **12**. In isolation, the potassium alkoxides are expected to be higher energy species than the corresponding lithium alkoxides; therefore, the process may well be driven by the attainment of *t*-BuOLi or LiOTMS in preference to *t*-BuOK or KOTMS, respectively. Presumably, in the 3°-alkoxides and silanolates, the energy differences are most pronounced; however, it is difficult to account further for the exchange behaviour given the relatively complex aggregation dynamics of the various components present in solution. [14]

Having established straightforward access to dienyl alcohol **4**, IMDA precursor **2** (R = H) was assembled and the cycloaddition repeated to provide a reference sample of lactone **1**. [3g,h] With a view to achieving an enantioselective variant of this process, alternative additives and promoters were screened[15] but these resulted in no conversion of the starting material or, for example with BINOL/$Me_3Al$ or BINOL/$Me_2AlCl$ in toluene at 90 °C, only decomposition of the starting material. An attempt to achieve asymmetric organocatalysis of the cycloaddition[16] between 4-methylpent-2-enal **16**[17] (Figure 3) and diene **4** gave no product. Similarly unsuccessful was the diastereoselective DA reaction between diene **4** and dienophile **17**,[18] bearing Evans' chiral auxiliary, with either $Me_2AlCl$, $Cu(OTf)_2$, or $Yb(OTf)_3$ as Lewis acidic promoters. [19] Continuing the theme of a potential enantioselective *inter*molecular variant of the cycloaddition, encouraging close precedent was available in the reports by Ward[20] then Ishihara[21] on the reactions of methyl acrylate tethered temporarily to either sorbyl alcohol or its isomer, 4-methylpenta-2,4-diene, via a chiral bimetallic Lewis acid linker generated from MeMgBr/$Me_2Zn$ + either BINOL or octahydro-BINOL. Ward's work included the example of an isomer of diene **3**, with the authors noting that the reaction was slower, lower yielding, and resulted in a less enantioenriched product (ee = 82% vs. 93%); furthermore, from Ishihara's examples, the presence of the β-methyl group in a crotonate dienophile resulted in complete loss of reactivity. In the event, application of Ward's conditions, and variations, to the reaction of diene **4** and the ester dienophile **18** (2.0 equiv.) resulted, in most cases, in no significant cycloaddition. Product was formed only in four reactions: two with $Me_2AlCl$ (1.0 equiv.) in dichloromethane at either RT (6 d, 41%) or reflux (18 h, 29%), and two containing $Me_2AlCl$ (2.0 equiv.) and BINOL (1.0 equiv.) in dichloromethane at reflux (36 h, 15% or 18 h, 23% with a larger excess of ester **18**).

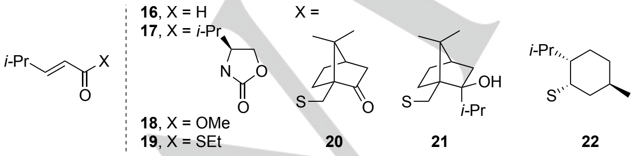
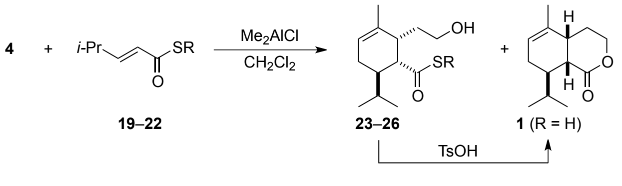


Figure 3. Dienophiles used for intermolecular DA cycloaddition with dienyl alcohol **4**.

These studies led to the conclusion that achieving an enantioselective IMDA reaction to form lactone **1** would be difficult, and intermolecular variants with dienophiles **16**–**18** had been similarly unpromising; a different approach was needed. The enhanced reactivity of thioesters as acylating agents, in comparison to normal esters, may be ascribed to a smaller loss of (S or O)p–(C=O)π* delocalisation in approaching the transition state for nucleophilic addition. [22] Indeed, the reactivity of the thioester carbonyl group is generally equated to that of analogous ketones, and this underpins the ubiquitous occurrence of thioesters in biological acylations. On this basis, it is reasonable to expect that thioesters would be more reactive DA dienophiles than the corresponding simple esters. The early literature contains passing mention of this aspect, [23] including the responsiveness of 3-thiolen-2-one[24] towards catalysis of its cycloaddition chemistry by $BF_3 \cdot OEt_2$ and, in separate work, preferential activation of thioester carbonyl functionality by *B*-bromocatechol borane. [25] Of most relevance, however, are four papers by Hart, [26] in the first of which it is noted that "there was surprisingly little known about DA reactions of unsaturated thioesters". Thioester variants of unsuccessful β-substituted ethyl and *tert*-butyl acrylate dienophiles were shown to react with octa-5,7-dienenitrile, albeit in low to moderate yields and poor *endo-*/*exo-* ratios following heating at 150 °C for ~24 h. [26a] In the later papers, mild reaction conditions were achieved using $Et_2AlCl$-$SiO_2$ or $TiCl_4$ and it was explicitly noted, for the first time, that "thioesters and selenoesters as dienophiles […] are more reactive than normal esters". [26d] Little synthetic application of this increased reactivity has been reported in the intervening two decades but this aspect was used to advantage recently during the synthesis of an α-helix mimetic scaffold in which a dihydropyridine, found to be unreactive towards cycloaddition with crotonate esters, was shown to react successfully with *S*-*tert*-butyl thiocrotonate. [27],[28]

Preliminary experiments with *S*-ethyl thioester **19**[29] showed that the reaction proceeded smoothly, albeit slowly, in dichloromethane at RT with $Me_2AlCl$ as Lewis acid (1.0 equiv.), generating a mixture of the *endo*-DA adduct **23** (Scheme 2) and lactone **1**; treatment with TsOH at the end of the reaction completed the cyclisation rapidly to afford solely the lactone. Running the reaction in the presence of racemic BINOL resulted in little change in the rate (~36 h) and yield (~65%) of the reaction, and no enantioenrichment was observed with (*R*)- or (*S*)-BINOL. [30] Other Lewis acid combinations ($Me_3Al$ with or without either MeMgBr or $Et_2Zn$) with BINOL proved ineffective even with extended reaction times (up to 11 d).



Scheme 2. Intermolecular thioester DA reactions with dienyl alcohol **4** then acid-mediated lactonisation. [31]

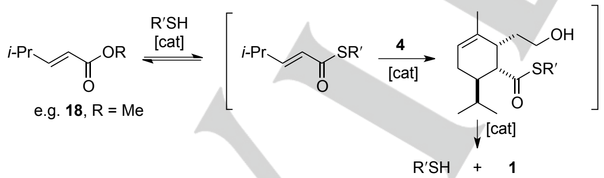
The ability to form lactone **1** under mild conditions suggested that a chiral thioester could impart diastereoselectivity to the DA step which would translate to enantiomeric enrichment following

TsOH-mediated lactonisation.[32] Three preliminary reactions gave encouraging results: (1) camphor thiol dienophile **20** showed similar reactivity to thioester **19** in its DA reaction with diene **4**, providing a 40 : 60 ratio of adduct **24** and lactone **1** from which a 66% isolated yield of lactone **1** was isolated with er = 72 : 28; (2) the camphor thiol variant **21**, incorporating 3°-alcohol rather than ketone functionality in the vicinity of the thioester, displayed a similar level of dienophile activation, but lower conversion in situ to the lactone (adduct **25** : lactone **1** = 65 : 35), and a poor er = 53.5 : 46.5; (3) thio-neomenthol dienophile **22** reacted very sluggishly and, after 6 d at RT, only the adduct **26** was present, in addition to starting material, from which a 30% yield of lactone **1** was isolated following TsOH treatment (er = 66 : 33). Clearly, further work is needed in order to optimise from the camphor thiol result but these first experiments suggest that relatively unhindered thiol precursors, bearing a second site for potential chelation with Lewis acids, would be good starting points for development.

## Conclusions

The one-step stereoselective synthesis of dienyl alcohol **4** has been made possible by the identification of an appropriate THF-soluble potassium salt that promotes $Li^+/K^+$ exchange and anion-accelerated [1,3]-shift in situ, free from base-mediated side-reactions. This convenient procedure could replace other reactions in which a first-formed unreactive metal alkoxide has to be protonated and then rearrangement promoted in a separate step by KH treatment. Attempts to achieve asymmetric catalysis of an IMDA reaction to form lactone **1** were unsuccessful but the same overall result has been achieved in this work by exploiting the increased reactivity of thioesters both as dienophiles and, subsequently, as acylating agents.

In view of the relative ease of DA reactions with thioester dienophiles compared with normal esters, and the possibility for catalysis of both the ester/thioester exchange and lactonisation steps, future research will explore direct formation of enantiomerically enriched lactones of the form **1** from readily-available unsaturated esters and acyclic dienes, using an optimised chiral thiol as a nucleophilic catalyst (Scheme 3).



Scheme 3. Proposed direct formation of enantioenriched lactone **1** from unsaturated esters using a chiral thiol R′SH coupled with a dual-purpose transacylation catalyst [cat].

## Experimental Section

**General Information:** All reactions were carried out under an argon atmosphere in dried glassware unless otherwise noted. 18-crown-6 was dried by stirring under high vacuum. TMSOK was dried by heating to 100 °C under high vacuum. $CeCl_3$ was dried by heating under high vacuum, first at 90 °C then at 140 °C. All other reagents were used as obtained from the supplier. "Petrol" refers to the fraction of petroleum ether boiling in the range 30–40 °C. Dichloromethane was obtained from an MBraun 5 solvent purification system. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone under a nitrogen atmosphere. Flash column chromatography was performed using Merck Geduran® silica gel (40–63 µm). Analytical thin-layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica gel (0.2 mm, Merck 60 F254), which were developed using $KMnO_4$. Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm and at 25 °C; concentrations (*c*) are expressed in g/100 mL. IR spectra were recorded as a thin film on a Bruker Tensor 27 FT-IR spectrometer. Proton ($^1H$) and carbon ($^{13}C$) NMR spectra were recorded on Bruker AVII-500 (500/125 MHz), Bruker AVIII-400 (400/100 MHz), or Bruker AV-400 (400/100 MHz) spectrometers. Chemical shifts ($\delta_H$ and $\delta_C$) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak; $^1H$–$^1H$ coupling constants (*J*) are rounded to the nearest 0.5 Hz. High-resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory on a Bruker Daltonics MicroTOF spectrometer; mass to charge ratios (*m/z*) are reported in Daltons. Chiral GC measurements were conducted on an HP6890 ($H_2$ as vector gas) or HP6850 ($H_2$ as vector gas) with a Lipodex® E column.

**(*E*)-4-Methylhexadien-1-ol (4):**[3e] To a cooled (–78 °C) solution of 3-methyl-1,4-pentadiene (2.00 mL, 16.5 mmol) in THF (45.0 mL) was added butyllithium (2.5 M solution in hexanes, 6.0 mL, 15 mmol) dropwise. The reaction mixture was allowed to warm to RT over 40 min, then cooled again to –78 °C, and paraformaldehyde (675 mg, 22.5 mmol) was added as a suspension in THF (5.0 mL). The mixture was allowed to warm to RT, and once reaction was complete (judged by disappearance of the red colouration of the organometallic species), 18-crown-6 was added (3.96 g, 15.0 mmol) followed by KOTMS (4.27 g, 30.0 mmol) as a solution in THF (5.0 mL). The solution was stirred at RT for 15 min then brine (30 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with water (30 mL) then brine (30 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude residue was purified by bulb-to-bulb distillation (110 °C at 20 mmHg) to give the title compound as a colourless oil (921 mg, 55%). $R_f$ 0.45 (petrol / ether, 1:1); $\delta_H$ (400 MHz, $CDCl_3$) 6.38 (dd, *J* = 17.5, 10.5 Hz, 1 H), 5.49 (t, *J* = 7.5 Hz, 1 H), 5.12 (d, *J* = 17.5 Hz, 1 H), 4.97 (d, *J* = 10.5 Hz, 1 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 2.42 (app. q, *J* = 7.0 Hz, 2 H), 1.96 (br s, 1 H), 1.77 (s, 3 H); $\delta_C$ (100 MHz, $CDCl_3$) 141.2, 136.7, 128.4, 111.5, 62.2, 31.9, 12.0.

**(1*S*,2*S*,4*R*)-2-Isopropyl-1-(mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (S1):** The thiol required for the synthesis of thioester **21** was prepared following a literature procedure for a similar compound.[32b] $CeCl_3$ (750 mg, 3.04 mmol) was suspended in THF (2.0 mL) and the mixture was sonicated for 30 min then stirred for 15 min. The mixture was cooled to –78 °C, then isopropylmagnesium chloride (2.0 M solution in THF, 1.5 mL, 3.0 mmol) was added dropwise; the mixture was stirred for 2 h at –78 °C then a solution of camphor thiol (175 mg, 0.950 mmol) in THF (2.0 mL) was added. The reaction mixture was allowed to warm to RT then stirred for 18 h, quenched with hydrochloric acid (1.0 M, 2.0 mL) and extracted with petrol (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (petrol / ether, 19:1) to give the *title* *compound* as a colourless oil (120 mg, 55%). $[\alpha]_D$ = –1.7 (*c* = 1.0, $CHCl_3$); $R_f$ 0.29 (petrol / ether, 9:1); $\nu_{max}$ (thin film)/$cm^{-1}$ 3504br, 2949s, 1456m, 1386m, 1029m, 984m; $\delta_H$ (400 MHz, $CDCl_3$) 2.93 (dd, *J* = 14.5, 7.5 Hz, 1 H), 2.83 (dd, *J* = 14.5, 8.5 Hz, 1 H), 2.02 (s, 1 H), 1.94 (ddd, *J* = 13.0, 4.5, 3.0 Hz, 1 H), 1.89–1.70 (m, 3 H), 1.64 (t, *J* = 4.5 Hz, 1 H), 1.44 (d, *J* = 13.0 Hz, 1 H) overlaying 1.43 (ddd, *J* = 12.5, 10.0, 2.5 Hz, 1 H), 1.39 (dd, *J* = 8.5, 7.5 Hz, 1H), 1.22 (s, 3 H), 1.08–1.00 (m, 1 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 0.97 (s, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H); $\delta_C$ (100 MHz, $CDCl_3$) 84.1, 54.5, 51.6, 47.8, 45.3, 37.3, 27.4, 27.2, 23.1, 22.3, 22.2, 18.4, 18.1; HRMS ($ESI^-$) found 227.1472, $C_{13}H_{23}OS$ $[M–H]^-$ requires 227.1475.

**General procedure for the preparation of thioesters 20–22:** To a solution of the thiol (x mmol) and 4-methyl-2-pentenoic acid (1.2x mmol) in dichloromethane (5.0x mL) was added DCC (1.3x mmol) and DMAP (0.1x mmol). The reaction mixture was stirred for 18 h at RT, filtered through Celite®, and washed with satd. aq. $NaHCO_3$ solution then brine. The organic portion was then dried ($MgSO_4$), the solvent was removed *in vacuo*, and the crude residue was purified by flash chromatography.

**(*E*)-*S*-[(1*R*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methyl 4-methylpent-2-enethioate (20):** Obtained as a colourless oil (462 mg, 82%) following flash chromatography (petrol / ether, 9:1). $[\alpha]_D$ = –53.7 (*c* = 1.00, $CHCl_3$); $R_f$ 0.39 (petrol / ether, 8:2); $\nu_{max}$ (thin film)/$cm^{-1}$ 2961m, 1742s, 1670m, 1629m, 1038m, 777m; $\delta_H$ (400 MHz, $CDCl_3$) 6.88 (dd, *J* = 15.5, 6.5 Hz, 1 H), 6.06 (dd, *J* = 15.5, 1.5 Hz, 1 H), 3.23 (d, *J* = 14.0 Hz, 1 H), 2.98 (d, *J* = 14.0 Hz, 1 H), 2.44 (octd, *J* = 7.0, 1.5 Hz, 1 H), 2.38 (ddd, *J* = 18.5, 4.5, 3.0 Hz, 1 H), 2.09 (t, *J* = 4.5 Hz, 1 H), 2.02–1.92 (m, 1 H), 1.87 (d, *J* = 18.5 Hz, 1 H) overlaying 1.84 (td, *J* = 13.5, 3.5 Hz, 1 H), 1.53 (ddd, *J* = 14.0, 9.5, 4.5 Hz, 1 H), 1.35 (ddd, *J* = 12.5, 9.5, 3.5 Hz, 1 H), 1.07 (s, 3 H), 1.06 (d, *J* = 7.0 Hz, 6 H), 0.92 (s, 3 H); $\delta_C$ (100 MHz, $CDCl_3$) 217.4, 190.7, 151.6, 125.9, 60.8, 48.0, 43.8, 43.1, 31.1, 26.8, 26.7, 24.6, 21.3 (two peaks), 20.2, 19.8; HRMS ($ESI^+$) found 281.1569, $C_{16}H_{25}O_2S$ $[MH]^+$ requires 281.1570.

**(*E*)-*S*-[(1*R*,2*S*,4*R*)-2-Hydroxy-2-isopropyl-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl 4-methylpent-2-enethioate (21):** Obtained as a colourless oil (180 mg, 69%) following flash chromatography (petrol / ether, 19:1). $[\alpha]_D$ = –1.6 (*c* = 0.45, $CHCl_3$); $R_f$ 0.49 (petrol / ether, 7:3); $\nu_{max}$ (thin film)/$cm^{-1}$ 3525br, 2961s, 1662s, 1628s, 1038s, 749m; $\delta_H$ (500 MHz, $CDCl_3$) 6.87 (dd, *J* = 15.5, 6.5 Hz, 1 H), 6.07 (dd, *J* = 15.5, 1.5 Hz, 1 H), 3.48 (d, *J* = 14.5 Hz, 1 H), 3.17 (d, *J* = 14.5 Hz, 1 H), 2.44 (octd, *J* = 6.5, 1.5 Hz, 1 H), 1.95 (ddd, *J* = 13.0, 4.5, 2.5 Hz, 1 H), 1.81 (sept, *J* = 6.5 Hz, 1 H), 1.78–1.65 (m, 2 H), 1.62 (t, *J* = 4.5 Hz, 1 H), 1.46 (d, *J* = 13.0 Hz, 1 H) overlaying 1.49–1.43 (m, 1 H), 1.20 (s, 3 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.07 (d, *J* = 6.5 Hz, 6 H), 1.13–1.03 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.94 (s, 3 H); $\delta_C$ (125 MHz, $CDCl_3$) 190.9, 151.1, 126.0, 83.8, 54.8, 51.7, 47.6, 45.1, 37.3, 31.1, 27.4, 27.2, 26.5, 22.4, 22.0, 21.3 (two peaks), 18.6, 18.2; HRMS ($ESI^+$) found 347.2014, $C_{19}H_{32}NaO_2S$ $[MNa]^+$ requires 347.2015.

**(*E*)-*S*-(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-methylpent-2-enethioate (22):** Obtained as a colourless oil (207 mg, 77%) following flash chromatography (petrol / ether, 19:1). $[\alpha]_D$ = +64.7 (*c* = 1.00, $CHCl_3$); $R_f$ 0.84 (petrol / ether, 8:2); $\nu_{max}$ (thin film)/$cm^{-1}$ 2956m, 1673s, 1630m, 1036s, 776s; $\delta_H$ (400 MHz, $CDCl_3$) 6.86 (dd, *J* = 15.5, 6.5 Hz, 1 H), 6.05 (dd, *J* = 15.5, 1.5 Hz, 1 H), 4.18 (qd, *J* = 3.5, 2.0 Hz, 1 H), 2.44 (octd, *J* = 7.0, 1.5 Hz, 1 H), 1.85 (app. dq, *J* = 13.5, 3.0 Hz, 2 H), 1.76–1.70 (m, 1 H), 1.70–1.59 (m, 1 H), 1.49–1.39 (m, 1 H), 1.35 (ddd, *J* = 13.5, 12.0, 3.5 Hz, 1 H), 1.15 (ddt, *J* = 11.5, 9.5, 3.5 Hz, 1 H), 1.07 (d, *J* = 7.0 Hz, 6 H), 1.03–0.92 (m, 2 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H); $\delta_C$ (100 MHz, $CDCl_3$) 190.0, 150.9, 126.6, 47.9, 44.9, 42.2, 35.2, 31.1, 30.7, 28.3, 28.0, 22.3, 21.4, 21.1, 20.9; HRMS ($ESI^+$) found 269.1934, $C_{16}H_{29}OS$ $[MH]^+$ requires 269.1939.

**(±)-(4a*R**,8*R**,8a*R**)-8-Isopropyl-5-methyl-3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one (1):**[3d,g] To a solution of alcohol **4** (28.0 mg, 0.250 mmol) and thioester **19** (160 mg, 1.01 mmol) in dichloromethane (2.0 mL) was added a solution of dimethylaluminium chloride (1.0 M solution in hexanes, 250 μL, 0.25 mmol). The reaction mixture was stirred at RT for 48 h, diluted with dichloromethane (5.0 mL), then satd. aq. Rochelle salt solution (10 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, the aqueous layer extracted with dichloromethane (3 × 10 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. The resulting mixture of adduct **23** and lactone **1** was dissolved in dichloromethane (2.0 mL) and *p*-toluenesulfonic acid monohydrate (24.0 mg, 0.126 mmol) was added. Stirring was continued for 3 h at RT, then the mixture was diluted with dichloromethane (5.0 mL), satd. aq. $NaHCO_3$ solution (10 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the so-formed residue was purified by flash chromatography (petrol / ether, 9:1 → 1:1) to give lactone **1** as a pale yellow oil (35.0 mg, 67%). $R_f$ 0.11 (petrol / ether, 4:1); $\delta_H$ (400 MHz, $C_6D_6$) 5.25 (br s, 1 H), 3.67 (ddd, *J* = 11.5, 7.5, 5.0 Hz, 1 H) 3.57 (dddd, *J* = 11.5, 5.5, 4.5, 1.0 Hz, 1 H), 2.50 (ddd, *J* = 6.5, 4.5, 1.5 Hz 1 H), 2.28–2.17 (m, 1 H), 2.10 (dtd, *J* = 9.0, 5.0, 3.5 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.87–1.77 (m, 1 H), 1.48 (ddt, *J* = 13.5, 9.0, 6.5 Hz, 1 H), 1.30 (dtd, *J* = 2.5, 1.5, 1.0 Hz, 3 H), 1.22–1.17 (m, 2 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H); $\delta_C$ (125 MHz, $C_6D_6$) 172.6, 132.5, 124.0, 65.6, 43.1, 39.5, 33.1, 27.1, 26.1, 24.6, 21.0, 20.5, 20.4.

**Diastereoselective Diels–Alder reactions with thioesters 20–22:** Reactions were run according to the procedure with *S*-ethyl thioester **19** but with an excess of alcohol **4** (2.0 equiv.) and dimethylaluminium chloride (2.0 equiv.) with respect to the thioester **20**–**22**. The enantiomeric ratio of the resulting lactone **1** was determined by chiral GC [Lipodex® E column; flow: 3.6 mL/min; 10 min at 50 °C, then +2 °C $min^{-1}$ to 170 °C, hold for 10 min, then +10 °C $min^{-1}$ to 220 °C, hold for 10 min; major enantiomer, $t_R$ = 67.6 min; minor enantiomer, $t_R$ = 68.3 min]. From the reaction with thioester **20**, lactone **1** was found to be enriched in the (+)-enantiomer (er = 72 : 28); $[\alpha]_D$ = +3.7 (*c* = 0.9, $CHCl_3$).

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**Keywords:** Thioesters • Diels–Alder reactions • Metal alkoxides • Sigmatropic shift • Lactones

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[31] The depictions of stereochemistry around the cyclohexenyl ring in **23**–**26** and **1** refer to relative configurations only; adduct **23** (R = Et) and lactone **1** produced from it are racemic, whereas adducts **24**–**26** (that derive from enantiomerically pure thiols) are enriched in one diastereomer and the derived lactone **1** is similarly enriched in the (+)-enantiomer.

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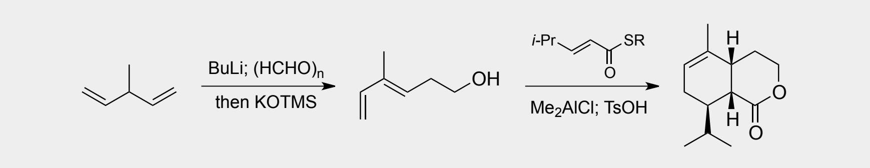

A one-step synthesis of (*E*)-4-methylhexa-3,5-dien-1-ol is presented in which metal counterion exchange of ROLi → ROK is effected in situ to promote oxy-anion accelerated [1,3]-sigmatropic shift. Exploitation of the heightened reactivity of thioesters as dienophiles and acylating agents allows exclusive *endo*-Diels–Alder reaction with this dienyl alcohol and subsequent lactonisation. Use of chiral thioesters leads to enantiomerically enriched lactone.

**Synthetic methods***

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***1 – 6***

**Synthesis of (*E*)-4-methylhexa-3,5-dien-1-ol and its Diels–Alder reaction with thioester dienophiles: a short enantioselective synthesis of bicyclic lactones**