First Total Synthesis and Structural Confirmation of C13-Butylrubber Oligomers

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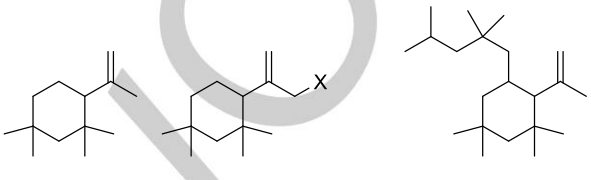
Abstract: The first total synthesis of an important C13 butyl rubber oligomer is reported. The structure of the oligomer, which is an important and potentially toxic extractable and leachable component of elastomeric closures, is confirmed by synthesis for the first time. The method described is scalable, making large quantities of the oligomer available for the first time for AMES toxicity studies. The challenging synthesis commences with isophorone and the key steps of the synthesis involve the development of highly novel dithoacetal chemistry, cuprate addition and Tebbe olefination.

Dedicated with deep fondness and respect to Professor Istvan E. Markó (1956-2017), who liked a challenging total synthesis!

Introduction

Elastomeric or rubber closures ('seals') have found widespread application, particularly in the pharmaceutical industry, frequently as components for injection systems, such as in stoppers and caps Elastomeric closures are particularly attractive and widely used owing to a number of beneficial features, including their ability to reseal. However, the composition of such rubbers is highly complex and may comprise many components, including the elastomer (basic unit) as well as anti-oxidants, fillers, curing agents, activators and accelerators. While the production of the rubbers has improved greatly over the last 30 years, there still remains the problems of impurities within the rubbers, and the potential for leaching of materials from the rubbers into the vial contents.

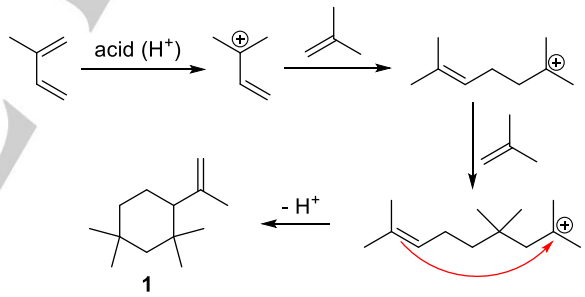
A series of C13 and C21 oligomers, together with their halogenated derivatives, have long been postulated as the key extractable components.[1] Through a large-scale rubber-extraction/isolation/purification technique, sufficient material has been isolated to determine the molecular formulae of these oligomers as $C_{13}H_{24}$ and its halogenated derivatives $C_{13}H_{23}Br$ or $C_{13}H_{23}Br$, and $C_{21}H_{40}$. Furthermore, the structures of the oligomers have been proposed to be (**1-3**) on the basis of extensive NMR studies.[1, 2]



C13 oligomer $C_{13}H_{24}$ **1** | C13 oligomer **2a** X = Cl **2b** X = Br | C21 oligomer $C_{21}H_{40}$ **3**

Figure 1. Proposed structures of butyl rubber oligomers.

It is proposed that these oligomers are formed during the polymerization process by an intramolecular cyclisation process, combining one isoprene and two isobutylene units (Scheme 2).



Scheme 1. Proposed mechanism of formation of the $C_{13}H_{24}$ oligomer.

Compounds (**1**) and (**3**) have recently become commercially available and are obtained via extraction and purification from a large number of rubber seals![2] It is reported that they can be present in quantities between 0.05 – 0.6 g per kg material. Extractable and leachable studies have shown that in certain instances, these may leach out of the rubber and into the drug product. Crucially, there is no toxicity data about these compounds, mainly owing to being only ever isolated in these minute quantities. A completed syntheses of these compounds is therefore urgent, both for verification of the structural assignments and to provide sufficient material for further toxicological evaluation via AMES tests. Herein, we report the first total synthesis of the C13 oligomer, (**1**) by a robust and scalable route.

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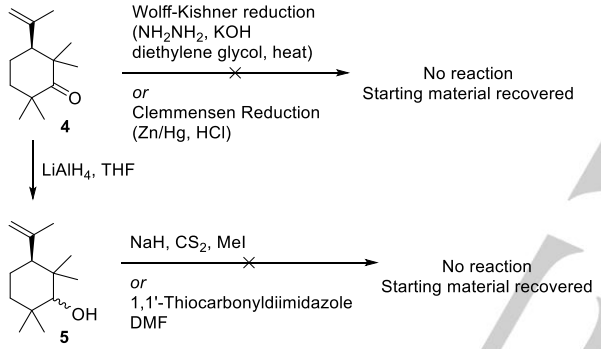
Results and Discussion

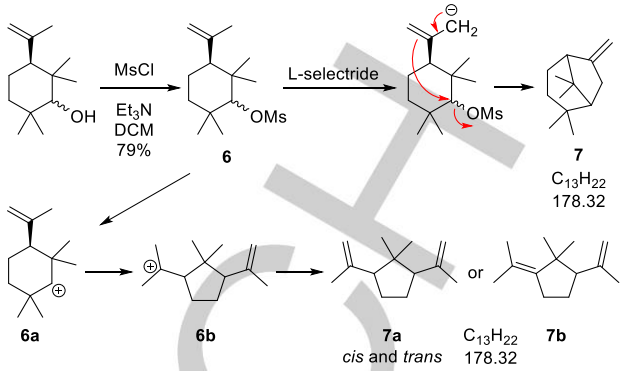
Obtaining the 1,2,4-substitution pattern was considered challenging from the outset, particularly given the steric bulk presented by the four methyl groups. A number of commercial compounds contain the two gem-dimethyl groups in the correct arrangements and were initially deemed to be suitable starting materials.

It is possible to access 3-(2-propenyl)-2,2,6,6-tetramethylcyclohexanone starting (**4**) from carvone.[3] Regrettably, all attempts to remove the carbonyl group were unsuccessful. Direct reduction of the ketone via Wolff-Kishner or Clemmensen reductions only gave unreacted starting material. Formation of a cyclic dithioacetal using ethane-1,2-dithiol, for subsequent reduction, was also unsuccessful, again with quantitative recovery of starting material. Lithium aluminium hydride reduction did give the corresponding alcohol (**5**), although attempts to remove this using radical methods were again unfruitful, with the alcohol unreactive under all attempted conditions (Scheme 2).



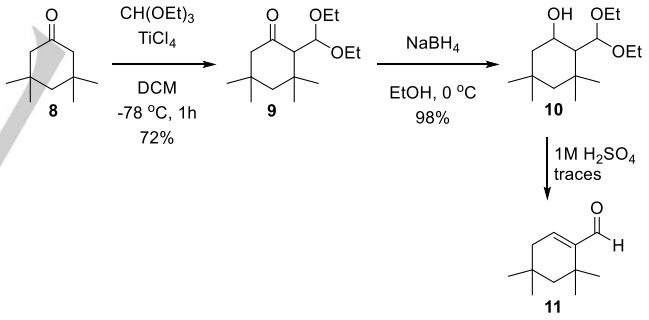
Scheme 2. Unsuccessful methods towards (**1**) starting from 3-(2-propenyl)-2,2,6,6-tetramethylcyclohexanone.

It was possible to produce the mesylate (**6**) derived from (**5**), but not the tosylate (Scheme 3). Treatment with sodium borohydride or lithium aluminium hydride to displace the mesylate gave no reaction. Reaction of (**6**) with L-selectride gave a product lacking in the mesyl moiety and containing a terminal alkene, which was initially believed to be the desired target (**1**). GC-MS analysis showed two close running compounds, both giving identical mass spectra but with *m/z* = 178.32, two mass units less than the proposed compound (**1**). Extensive NMR studies suggested that rather than reduction, the hydride had deprotonated the allylic-CH_3 group, which lead to intramolecular displacement of the mesylate to furnish the bridged cycloalkane (**7**), with the correct observed molecular weight. However, from the NMR spectra, it is impossible to discount the alternative structures (**7a** or **7b**), formed *via* direct S_N1-type loss of the mesylate followed by carbocation rearrangement/ring contraction to the more stable carbocation and elimination, to give the various possible 5-membered ring products (Scheme 3).



Scheme 3. Attempted mesylate displacement leading either to bicyclic product (**7**) or rearranged product (**7a/7b**).

With no other suitable 1,2,4-substituted precursors being commercially available, ketone (**8**) was seen as a suitable starting material. Introduction of the formyl group, masked as an acetal, was facile and high yielding employing triethyl orthoformate and $TiCl_4$ (**9**, 72 %). However, all attempts to remove the ketone were unsuccessful. Wolff-Kishner conditions, either with hydrazine or TBS-protected hydrazine, gave no reaction. Sodium borohydride reduction did afford the alcohol (**10**) in excellent yield, but regrettably any attempts to remove this either showed no reaction or gave a product suggestive of polymerization. Only treatment with dilute sulfuric acid gave any traces of the elimination product (**11**), and not in yields to be of any use.



Scheme 4. Attempted route to (**1**) starting from 3,3,5,5-tetramethylcyclohexanone.

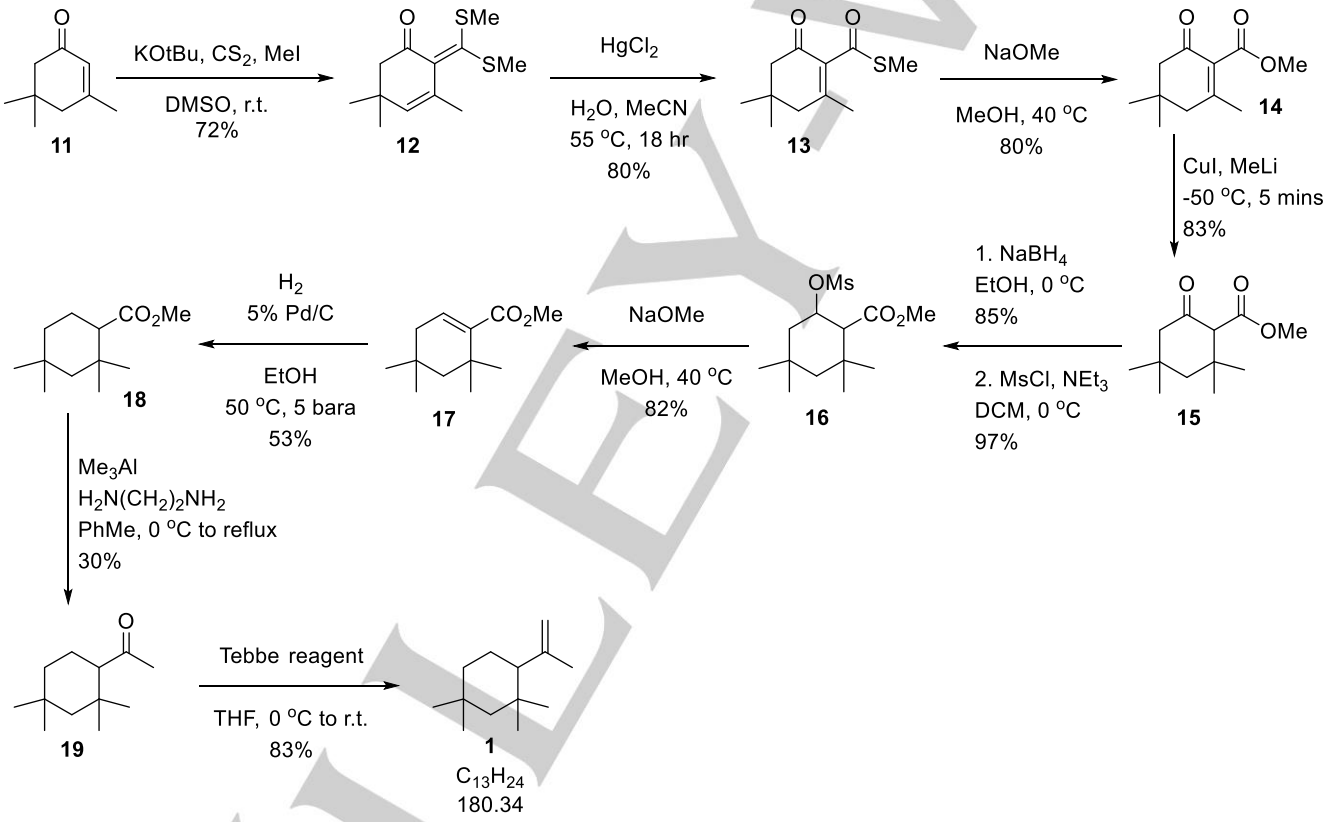
The problems encountered in all these approaches were attributed to the two gem dimethyl groups present in the different starting materials. Therefore a novel approach was required that would not rely upon late stage removal of a ketone moiety. It was also envisaged that any successful route would not have the four problematic methyl groups present throughout the synthesis, but rather would introduce these at an appropriate stage in the synthesis.

It was proposed to employ an α-oxoketene dithioacetal,[4-6] derived from carbon disulfide, as the solution for introducing the required side chain, and then to introduce one of the problematic gem-dimethyl groups at a later stage in the synthesis, once all

necessary functional group interconversions were complete (Scheme 4). Starting from isophorone (**11**), reaction with potassium *tert*-butoxide and carbon disulfide installed the dithioacetal moiety (**12**), and $HgCl_2$-mediated hydrolysis[6] gave the thioester (**13**) in 58% yield over the two steps. Treatment with sodium methoxide furnished the methyl ester (**14**) in 80% yield.[7] It was at this stage that methyl cuprate addition to the α,β-unsaturated system installed the fourth methyl group (**15**), obtained as a mixture of keto-enol tautomers (approximate 1.5:1 ratio). Reduction of the ketone with sodium borohydride proceeded smoothly as before, and this was protected as the mesylate, (**16**). Unlike before, elimination of the mesylate proceeded smoothly, presumably owing to the α,β-unsaturated product (**17**) that was formed. Reduction of the alkene was achieved by hydrogenation in ethanol over 5% w/w palladium on charcoal. Reaction of the ester with trimethyl aluminium/TMEDA gave the ketone (**18**). This was finally converted to the alkene using the Tebbe reagent, to give the postulated C13 oligomer (**1**) in 10 steps and 3.4% overall yield. The new terminal alkene peaks were clearly visible at δ = 4.64 and 4.82 ppm, which were completely in agreement with the literature values.[1]

Comparison of the NMR and mass spectra of (**1**) with a genuine sample of (**1**) and previously reported values[1] confirmed that, for the first time, the C13 oligomer had been prepared synthetically away from the polymerisation approach. The two mass spectra were identical, both in the molecular ion and fragmentation pattern obtained. Therefore the proposed structure of (**1**) has finally been unambiguously confirmed by synthesis.

It was possible to prepare the chloro-derivative (**2a**) using the procedure of Brindisi et al, employing cerium trichloride and NaOCl.[8]



Scheme 5. Total synthesis of the C13 oligomer, **1**.

Conclusions

In conclusion, we have reported the first *de novo* total synthesis of the C13 extractable/leachable oligomer, **1**. In completing the synthesis, we have also confirmed the proposed structure for this compound. The synthesis is robust and scalable, and provides material for extensive toxicity studies, in order to evaluate the potential dangers of this extractable and leachable compound in medical applications.

Experimental Section

2-(Bis(methylthio)methylene)-3,5,5-trimethylcyclohex-3-en-1-one (12)

To a solution of potassium *tert*-butoxide (24.69 g, 220 mmol, 2.2 equiv) in dry DMSO (200.0 ml), isophorone **11** (13.82 g, 100.0 mmol, 1.0 equiv) was added portionwise and the dark red solution was stirred at room temperature for 30 minutes. Carbon disulfide (8 g, 105.0 mmol, 1.05 equiv) was added in one portion (careful: very exothermic) and the dark brown solution was stirred for 30 minutes. Iodomethane (31.22 g, 220 mmol, 2.2 equiv) was added (careful: very exothermic) and the dark brown reaction was stirred at room temperature for 1 h. Water (20 ml) and Et_2O (40 ml) were added to the reaction and the organic layer was separated and washed with saturated brine solution (20 ml). The aqueous layers were combined and extracted with Et_2O (10 x 20 ml). The organic layers were combined, dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 10% Et_2O in Petrol, R_f = 0.3) to give the mixture of the two tautomers (*endo*:*exo* 92:8) of the *title compound* as a red thick oil (17.45 g, 72%); *major tautomer*: IR (cm^{-1}) 1650, 1428, 1382,1362, 1339, 1300, 1253, 1197, 1137, 1115, 1045, 1005; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (d, *J* = 1.7 Hz, 1H), 2.41 (s, 3H), 2.31 (s, 2H), 2.24 (s, 3H), 2.08 (d, *J* = 1.7 Hz, 3H), 1.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 151.9, 139.2, 133.0, 132.0, 51.7, 33.2, 28.5, 20.3, 19.9, 18.9; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{12}H_{19}OS_2$ requires 243.0872; found, 243.0868.

***S*-Methyl 2,4,4-trimethyl-6-oxocyclohex-1-ene-1-carbothioate (13)**

To a dark red solution of 2-(bis(methylthio)methylene)-3,5,5-trimethylcyclohex-3-en-1-one **12** (17.45 g, 72 mmol, 1.0 equiv) in water (20 ml) and acetonitrile (120 ml), $HgCl_2$ was added (21.50 g, 79.2 mmol, 1.1 equiv) and the reaction was stirred at 55 °C until the starting material was completely consumed. The dark green/brown suspension was allowed to cool down to room temperature, filtered through a silica plug and the acetonitrile was removed at reduced pressure. The aqueous layer was extracted with dichloromethane (2 x 50 ml), dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 10% EtOAc in Petrol, R_f = 0.1) to give the *title compound* as a crystalline yellow solid (12.23 g, 80%); m.p.: 98-102 °C; IR (cm^{-1}) 1659, 1621, 1422, 1377, 1359, 1308, 1150, 1113, 1023; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.25 (s, 2H), 2.24 (s, 2H), 1.93 (s, 3H), 1.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 194.2, 158.4, 137.1, 50.8, 46.2, 32.9, 28.2, 22.2, 12.2; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{11}H_{17}O_2S$ requires 213.0944; found, 213.0943.

Methyl 2,4,4-trimethyl-6-oxocyclohex-1-ene-1-carboxylate (14)

A solution of NaH (1.14 g, 60 mmol, 1.04 equiv) in dry MeOH (50 ml) at 0 °C was transferred to a solution of *S*-methyl 2,4,4-trimethyl-6-oxocyclohex-1-ene-1-carbothioate **13** (12.23 g, 57.6 mmol, 1.0 equiv) in dry MeOH (50 ml) and stirred at 40 °C until the starting material was consumed. The reaction was allowed to cool down to room temperature, then a saturated solution of NH_4Cl (20 ml) was added and the solvent was removed at reduced pressure. The aqueous layer was extracted with dichloromethane (2 x 50 ml), dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 10% EtOAc in Petrol, R_f = 0.05) to give the *title compound* as a colourless oil (9.04 g, 80%); IR (cm^{-1}) 1732, 1667, 1634, 1435, 1378, 1369, 1320, 1279, 1239, 1196, 1143, 1068, 1023; ^1H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 2.25 (s, 2H), 2.25 (s, 2H), 1.94 (s, 3H), 1.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 167.3, 158.6, 131.9, 52.2, 50.6, 45.9, 33.0, 28.2, 22.5; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{11}H_{17}O_3$ requires 197.1172; found, 197.1170.

Methyl 2,2,4,4-tetramethyl-6-oxocyclohexane-1-carboxylate (15)

A suspension of CuI (9.65 g, 60.69 mmol, 1.1 equiv) in dry Et_2O (100 ml) was cooled to −50 °C. Methyl lithium solution (1.6 M in Et_2O, 75.86 ml, 121.4 mmol, 2.2 equiv) was added and the reaction was left stirring at −50 °C for 30 minutes. A solution of methyl 2,4,4-trimethyl-6-oxocyclohex-1-ene-1-carboxylate **14** (9.04 g, 46.08 mmol, 1.0 equiv) in dry Et_2O (40 ml) was added dropwise and the reaction was stirred at −50 °C until the starting material was consumed. A saturated solution of NH_4Cl (20 ml) was added and the reaction was allowed to warm up to room temperature, before filtering through a silica pad. The organic layer was separated, dried with $MgSO_4$, filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 1% Et_2O in Petrol, R_f = 0.5) to give the *title compound* as a colourless oil (8.118 g, 83%); *major tautomer*: IR (cm^{-1}) 1755, 1733, 1710, 1633, 1599, 1459, 1436, 1391, 1371, 1344, 1316, 1276, 1229, 1197, 1154, 1098, 1037; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.15 (s, 1H), 2.57 (d, *J* = 13.0 Hz, 2H), 2.32 (d, *J* = 13.0 Hz, 2H), 1.85 (d, *J* = 14 Hz, 2H), 1.45 (d, *J* = 14.0 Hz, 2H), 1.07 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 169.3, 66.4, 52.4, 51.8, 50.4, 39.2, 35.9, 31.7, 31.6, 31.0, 27.3; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{12}H_{21}O_3$ requires 213.1485; found, 213.1483.

Methyl 6-hydroxy-2,2,4,4-tetramethylcyclohexane-1-carboxylate

To a solution of methyl 2,2,4,4-tetramethyl-6-oxocyclohexane-1-carboxylate **15** (8.12 g, 38.24 mmol, 1.0 equiv) in dry MeOH (50 ml) at 0 °C, was added $NaBH_4$ (1.74 g, 45.89 mmol, 1.2 equiv) and the reaction stirred until the starting material was consumed. A saturated solution of NH_4Cl (20 ml) was added and the solvent removed at reduced pressure. The aqueous layer was extracted with Et_2O (3 x 30 ml), dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 10% EtOAc in Petrol, R_f = 0.3) to give the mixture of the two diastereomers of the *title compound* as a white solid (6.97 g, 85%). This was used immediately in the next step.

Methyl 2,2,4,4-tetramethyl-6-((methylsulfonyl)oxy)cyclohexane-1-carboxylate (16)

To a solution of the two diastereomers of methyl 6-hydroxy-2,2,4,4-tetramethylcyclohexane-1-carboxylate (6.97 g, 32.50 mmol, 1.0 equiv) in dichloromethane (50 ml) at 0 °C, triethylamine (4.77 g, 47.13 mmol, 1.45 equiv) and methanesulfonyl chloride (5.58 g, 48.75 mmol, 1.5 equiv) were added and the reaction was left stirring for 3 h. The reaction was allowed to warm up to room temperature, then a saturated solution of NH_4Cl (20 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 30 ml), the organic layers were combined, dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 10% EtOAc in Petrol, R_f = 0.3) to give the mixture of the two diastereomers of the *title compound* as a white solid (9.27 g, 97%). This was used immediately in the next step.

Methyl 4,4,6,6-tetramethylcyclohex-1-ene-1-carboxylate (17)

A solution of NaH (983 mg, 40.1 mmol, 1.3 equiv) in dry MeOH (50 ml) at 0 °C was transferred to a solution of methyl 2,2,4,4-tetramethyl-6-((methylsulfonyl)oxy)cyclohexane-1-carboxylate **16** (9.27 g, 31.52 mmol, 1.0 equiv) in dry MeOH (50 ml) and stirred at 40 °C until the starting material was consumed. The reaction was allowed to cool down to room

temperature, then a saturated solution of NH_4Cl (20 ml) was added and the solvent was removed at reduced pressure. The aqueous layer was extracted with dichloromethane (2 x 50 ml), dried with $MgSO_4$ filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 1% Et_2O in Petrol, R_f = 0.5) to give the *title compound* as a colourless oil (5.07 g, 82%); IR (cm^{-1}) 1707, 1459, 1436, 1366, 1249, 1190, 1062; ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 4.3 Hz, 1H); 1.94 (d, *J* = 4.3 Hz, 2H), 1.40 (s, 2H), 1.24 (s, 6H), 0.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 138.6, 136.7, 53.5, 51.2, 40.4, 33.7, 29.9, 29.8, 29.6; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{12}H_{21}O_2$ requires 197.1536; found, 197.1535.

Methyl 2,2,4,4-tetramethylcyclohexane-1-carboxylate (18)

Methyl 4,4,6,6-tetramethylcyclohex-1-enecarboxylate **17** (500 mg, 2.55 mmol), Pd/C 5% type 39 (250 mg, 0.5 wt) and ethanol (5.00 mL) were charged to each of 3 vessels of an HEL High Pressure ChemScan and hydrogenated at 50 °C, 5 bara for 5 h. Analysis by LCMS indicated incomplete conversion so the hydrogenation was continued for a further 16 h at 50 °C and 5 bara, after which all reaction were judged complete by LCMS. The three reaction mixtures were combined and filtered through Celite, washing through with ethanol (~15 mL). The filtrate was concentrated to an oil, during which a separate layer was observed. The material was redissolved in diethyl ether (~30 mL) and dried over Na_2SO_4 to remove any residual water then filtered and again concentrated, controlling the vacuum to no more than 200 mbar and the water bath to no more than 40 °C to minimise loss of product. A small amount of a separate phase was again observed, for which NMR showed broad signals corresponding to expected peaks for ethanol. This was removed by pipette to leave methyl 2,2,4,4-tetramethylcyclohexane-1-carboxylate (0.798 g, 4.03 mmol, 53%) as a colourless oil that was used directly in the next step. IR (cm^{-1}) 1733, 1458, 1434, 1388, 1365, 1325, 1293, 1248, 1213, 1172, 1147, 1034; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 3H); 2.07 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.82 (ddd, *J* = 27.2, 13.8 and 3.5 Hz, 1H), 1.60-1.54 (m, 1H), 1.47-1.41 (m, 1H), 1.27 (dd, *J* = 13.8, 2.5 Hz, 1H), 1.14-1.05 (m, 2H), 0.96 (s, 6H), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 54.0, 52.9, 51.0, 38.4, 34.5, 33.6, 33.2, 30.9, 27.2, 24.0, 22.6; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{12}H_{23}O_2$ requires 199.1693; found, 199.1691.

1-(2,2,4,4-Tetramethylcyclohexyl)ethan-1-one (19)

To a solution of *N*,*N*'-dimethylethylenediamine (265 mg. 3.00 mmol, 1.1 equiv) in toluene (20.0 ml) at 0 °C, a solution of trimethylaluminum (4.23 ml, 8.46 mmol, 2.0 M in toluene, 3.1 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 h before adding a solution of methyl 2,2,4,4-tetramethylcyclohexane-1-carboxylate **18** (541 mg, 2.73 mmol, 1.0 equiv) in toluene (5.0 ml). The resulting mixture was heated to reflux and was monitored *via* TLC (5% Et_2O in Petrol). The reaction mixture was cooled to room temperature and quenched with 1 N aqueous HCl solution. The organic layer was extracted with EtOAc (3 x 30 ml), dried with $MgSO_4$, filtered and the solvent was removed at reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 5% Et_2O in Petrol, R_f = 0.2) to give the *title compound* as a colourless oil (148 mg, 30%); IR (cm^{-1}) 1707, 1457, 1388, 1358, 1203, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (dd, *J* = 11.8, 3.0 Hz, 1H), 2.16 (s, 3H), 1.85-1.71 (m, 1H), 1.56-1.39 (m, 2H), 1.34-1.07 (m, 3H), 1.03-0.94 (m, 9H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 60.2, 54.6, 38.7, 34.5, 34.1, 33.4, 32.2, 31.0, 27.4, 23.9, 22.5; HRMS-ASAP (*m/z*) [M + H]+ calcd for $C_{12}H_{23}O$ requires 183.1743; found, 183.1741.

1,1,5,5-Tetramethyl-2-(prop-1-en-2-yl)cyclohexane (1)

To a solution of 1-(2,2,4,4-tetramethylcyclohexyl)ethan-1-one **19** (148 mg, 0.813 mmol, 1 equiv) in THF (5.0 ml) at 0 °C was added a toluene solution of the Tebbe reagent (4.87 ml, 2.44 mmol, 3 equiv). The reaction was allowed to stir at 0 °C for 15 minutes, then to room temperature for 1 h. The reaction was then cooled to 0 °C, diluted with Et_2O (5.0 ml) and washed with a 0.1 M aqueous solution of NaOH until gas evolution ceased. The reaction mixture was filtered through a silica pad, the organic layer extracted and dried over $MgSO_4$. The crude oil was purified by flash column chromatography (SiO_2, 2% Et_2O in Petrol, R_f = 0.6) to give the *title compound* as a colourless oil (121 mg, 0.67 mmol, 83%); IR (cm^{-1}) 1636, 1455, 1376; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83-4.80 (m, 1H), 4.63-4.60 (m, 1H), 1.77-1.64 (m, 5H), 1.49-1.42 (m, 1H), 1.38-1.32 (m, 1H), 1.27-1.11 (m, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 112.4, 55.6, 54.9, 40.3, 35.3, 34.7, 34.6, 31.3 27.0, 25.4, 23.8, 23.6; HRMS-EI (Waters GCT Premier Spectrometers) (*m/z*) [M] calcd for $C_{13}H_{24}$ requires 180.1878; found, 180.1877.

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Keywords: C13 butylrubber oligomer • dithioacetal • isophorone • Tebbe reagent • hydrogenation

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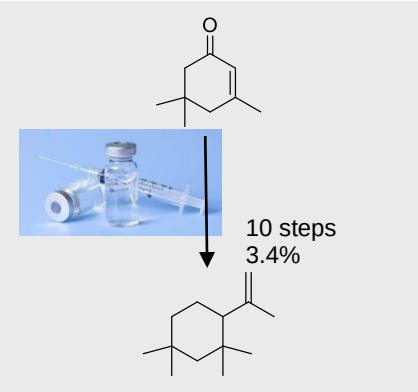
FULL PAPER

The first total synthesis of important C13 butyl rubber oligomers is reported. The structure of the oligomer, which is an important extractable and leachable component of elastomeric closures, is confirmed for the first time. The 10-step synthetic sequence starting from isophorone is robust and scalable, making large quantities of the oligomer available for the first time.



Extractable and leachable oligomers; C13-butyl rubber oligomers; total synthesis; structural confirmation; dithioacetal; Tebbe olefination

*Fabrizio Minicone, Robin Attrill, Michael Hodgson, Katherine Wheelhouse, Adrian Dobbs**

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First Total Synthesis and Structural Confirmation of C13-Butylrubber Oligomers