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Tetrahedron Letters 45 (2004) 8667–8671
Tetrahedron Letters

Formation of highly substituted chiral cyclohexanone derivatives using a tandem conjugate addition/cyclisation

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Received 26 August 2004; revised 17 September 2004; accepted 21 September 2004

Abstract—A tandem conjugate addition/cyclisation approach, that allows the synthesis of chiral highly substituted cyclohexanones and cyclohexenones, which is applicable to natural product syntheses has been developed.

Elysioidea sacoglossan molluscs are interesting marine organisms with the ability to sequester active chloroplasts from siphonaceous marine algae and retain these organelles in their tissues where they carry out photosynthesis.[1] These organisms have been the source of a number of novel polypropionate natural products (Fig. 1).[1–6]

Tridachiahydropyrone **1**,[2] 9,10-deoxytridachione **2**[3] and tridachiapyrone-A **3**[4] all possess a highly substituted cyclohexadiene ring. 9,10-Deoxytridachione **2** has been photochemically converted in vivo[1] and in vitro[3] into photodeoxytridachione **4**, whilst tridachiahydropyrone-B **5**[5] and –C **6**[5] appear to be photooxygenation products from tridachiahydropyrone **1**.

The function of these polypropionate metabolites in the organism is unclear, but it has been postulated that they may act as chemical defence agents against predation or exposure to UV light.[2,7] Tridachiapyrone-A **3** has been shown to be active against lymphocytic leukemia cells[4] but extraction from the natural source is not a viable option due to its low abundance.

Natural products of this type are yet to attract much attention from the synthetic community and only during the development of our synthetic approach was the first total synthesis of a member of this group of natural products reported by Miller and Trauner.[8] This elegant

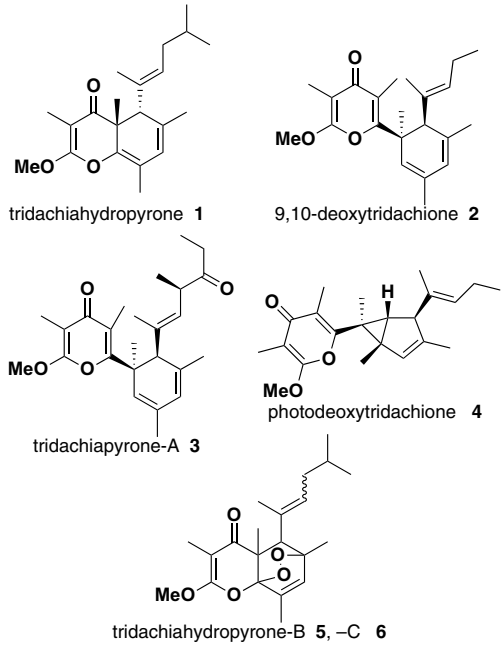

Figure 1.

approach to (±)-photodeoxytridachione **4** involved a Lewis acid catalysed cyclisation of the tetraene intermediate **7**. Thermal cyclisation of the same tetraene **7** gave the cyclohexadiene ring system present in 9,10-deoxytridachione **2** (Scheme 1).

Our approach relies on the formation of the highly substituted six-membered ring **8** as a single enantiomer by a

Keywords: Tridachiones; Conjugate addition; Tridachiahydropyrone.
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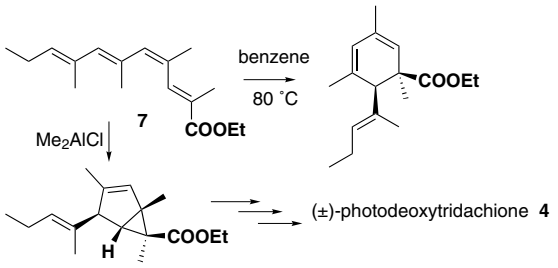
doi:10.1016/j.tetlet.2004.09.150



Scheme 1.

tandem conjugate addition–Dieckmann condensation.[9] In this approach we employ an Evans' chiral auxiliary[10] as the leaving group in the capture of the enolate formed by the conjugate addition to an α,β-unsaturated ketone or ester **9**. The chiral auxiliary also controls the aldol reaction, generating two of the stereocentres present in the acyclic precursor **9**. The stereocentres of **9** have the dual role of controlling the facial addition of the nucleophile in the Michael addition and of assisting in the cyclisation (by virtue of their equatorial orientation in the six-membered ring **8** that is formed). There are a limited number of reports of displacement of an Evans' chiral auxiliary by carbon nucleophiles in cyclisations.[11] Subsequent *axial* methylation and β-elimination leads to compound **10**, which could be further functionalised (Scheme 2).

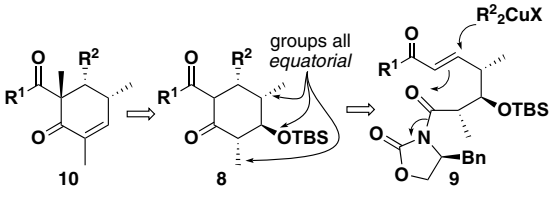
We now report the stereoselective synthesis of some highly substituted cyclohexanone and cyclohexenone derivatives using this strategy, that could be incorporated as the cyclohexadiene moiety found in members **1**–**3** of the tridachione family of marine natural products.

The model systems in which we chose to investigate this approach were the α,β-unsaturated ester **11** and the α,β-unsaturated ketone **12**. These two compounds were available from the same alcohol **13** by oxidation and reaction with the appropriate ylide (Scheme 3).

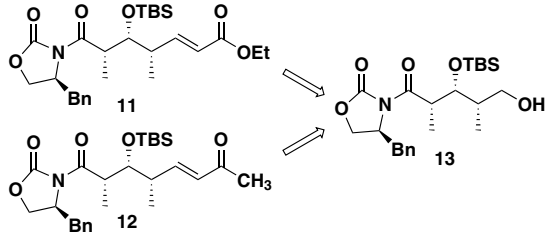
The alcohol **13** was prepared by the sequence shown in Scheme 3. Commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate was protected as the known PMB ether[12] **14** (83%) in multi-gram quantities using catalytic triflic acid (0.3 mol%) and PMB trichloroacetimidate[13] in ether. Small-scale reactions require significantly more acid catalyst. The product was distilled under reduced pressure[14] for larger scale reactions.

The ester **14** was reduced with $LiAlH_4$ (93%) and the crude product was subsequently oxidised under Swern conditions[15] with modified product isolation[16] to afford known aldehyde[12] **15** (99%, crude), which was sufficiently pure for the aldol reaction (Scheme 4). Treatment of the *N*-propionyl Evans' chiral auxiliary[10] **16** with dibutylboron triflate and Et_3N generated a *Z*-enolate, which underwent a *syn* aldol[10,17] coupling with crude aldehyde **15** to afford aldol adduct **17** (83%) with high diastereoselectivity (>95% ds by ^1H NMR). TBS protection[18] of **17** with TBSOTf/2,6-lutidine in CH_2Cl_2 yielded the diprotected product (97%), which was selectively deprotected with DDQ in CH_2Cl_2/pH 7 buffer[19] to give primary alcohol **13** (96%). Attempted purification by flash chromatography of **13** on silica led to complete conversion to known lactone **18**.[20] This showed the ability of the Evans' auxiliary to act as a leaving group in our system, even though it was an undesired side reaction at this stage. This problem was avoided by careful chromatography on buffered silica,[21] allowing purification of alcohol **13**.

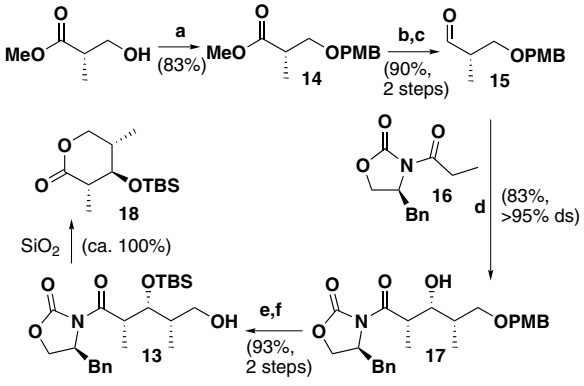
Alcohol **13** was cleanly oxidised (99%, crude) under Swern conditions[15,16] to aldehyde **19**, which has been produced on a multi-gram scale and is common to both



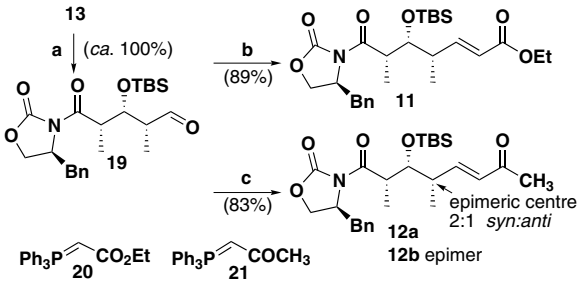
Scheme 2.



Scheme 3.



Scheme 4. Reagents and conditions: (**a**) PMB imidate (1.5 equiv), TfOH (0.3 mol%), Et_2O, rt, 45 min; (**b**) $LiAlH_4$ (1.1 equiv), THF, 0 °C → rt, 30 min; (**c**) (i) DMSO (3 equiv), $C_2O_2Cl_2$ (1.5 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) product from **b**, CH_2Cl_2, −78 °C, 45 min; (iii) Et_3N (6 equiv), −78 °C, 30 min → 0 °C; (**d**) (i) **16**, Bu_2BOTf (1.2 equiv), CH_2Cl_2, 0 °C, 30 min; (ii) Et_3N (1.3 equiv), 0 °C, 30 min; (iii) **15** (0.67 equiv), −78 °C, 30 min → 0 °C, 3–4 h; (**e**) 2,6-Lutidine (3 equiv), TBSOTf (1.5 equiv), CH_2Cl_2, 78 °C, 3–4 h; (**f**) DDQ (1.3 equiv), CH_2Cl_2, pH 7 buffer, 0 °C, 3.5 h.



Scheme 5. Reagents and conditions: (**a**) (i) DMSO (3 equiv), $C_2O_2Cl_2$ (1.5 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) **13**, CH_2Cl_2, −78 °C, 45 min; (iii) Et_3N (6 equiv), −78 °C, 30 min → 0 °C; (**b**) **20** (1.2 equiv), CH_2Cl_2, rt, 4 d; (**c**) **21** (1.2 equiv), toluene, 80 °C, 4 d.

our model studies (Scheme 5). Wittig coupling of aldehyde **19** with ylide **20** proceeded slowly at room temperature in CH_2Cl_2 to give **11** (89%) with high E-selectivity. The reaction of the aldehyde with ylide **21** was even more sluggish and required heating in toluene (Scheme 4). While this reaction gave **12** (83%) with high E-selectivity, unfortunately there were varying degrees of epimerisation of the stereocentre α to the aldehyde, leading to an inseparable epimeric mixture (2:1) of **12**. This mixture was used in subsequent reactions.

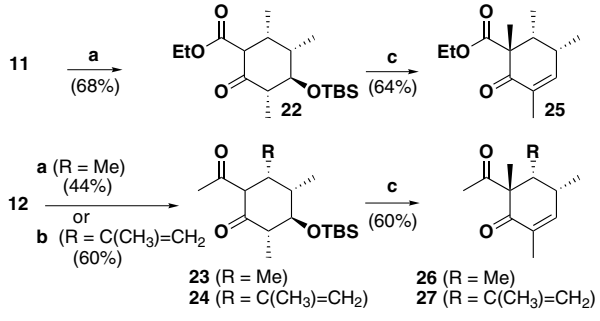
We proceeded to test the novel addition–cyclisation approach for the synthesis of the substituted cyclohexanones using dimethylcopperlithium. The enoate **11** was added dropwise at room temperature to dimethylcopperlithium[22] in a 1:1 mixture of ether and dimethylsulfide (Scheme 6). The reaction was complete within 1 h as determined by TLC analysis. Quenching (90% NH_4Cl/10% NH_4OH) and purification by chromatography yielded cyclic product **22** (68%), which contained varying mixtures of keto:enol tautomers. The presence of ^1H NMR signals for free Evans' auxiliary at $\delta = 5.86$, 4.43 and 2.88 ppm and the presence of the enol OH at $\delta = 12.34$ ppm (from the enol form of the product) in the crude reaction mixture were evidence for successful cyclisation.

The addition of dimethylcopperlithium to the enone **12** was carried out in an identical fashion giving, after purification, the product **23** in 44% yield as a single isomer. In this case the enol OH peaks occurred at $\delta = 16.43$ ppm and its presence in the crude reaction mixture was again indicative of a successful cyclisation. A minor epimeric product was separated that arose from the minor epimeric enone **12b**.

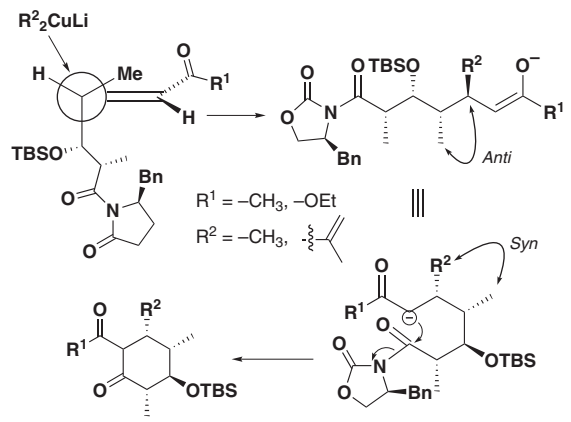
With success in the reactions involving dimethylcopperlithium we turned our attention to the addition of a cuprate derived from isopropenylmagnesium bromide, to emulate more closely the natural product vinyl side chains. The use of this cuprate proved to be problematic but we were able to add the cuprate to **12** and effect cyclisation using similar conditions to Boring and Sindelar[23] (Scheme 6). Addition of enone **12** to the cuprate at −78 °C, followed by warming to room temperature yielded a black insoluble mixture, but stirring overnight gave a pale yellow homogeneous solution. Quenching and purification afforded cyclic product **24** in 60% yield. As above, a minor epimeric product (from enone **12b**) was separated.

The stereochemistry of the new stereocentres formed in the addition/cyclisation was assigned by application of the experimental findings of Chounan et al.[24] on cuprate addition to unsaturated monoesters/ketones. These findings postulate a modified Felkin–Anh attack of the nucleophile (cuprate) to give an *anti* (or in our cyclic case, *syn*) relationship between the γ methyl and the newly formed stereocentre (Scheme 7).

The marine natural products **1**–**3** and others bear a *trans* relationship between the unsaturated side chain and an adjacent quaternary methyl group. The cyclic products **22**–**24** were methylated by treatment with NaH and MeI in THF at room temperature and under these conditions, with two or more equivalents of NaH there was also full elimination of the OTBS group to yield enones **25**–**27**[25] (Scheme 6). Elimination appears to occur both prior to and after methylation, as a range of products (methylated/saturated, methylated/unsaturated, not methylated/unsaturated) could be isolated depending on reaction time. Notably, *trans (axial)* methylation[26] was virtually exclusive for these simple enone/enoate systems with only a single isomeric product apparent



Scheme 6. Reagents and conditions: (**a**) (i) CuI (5 equiv), MeLi (10 equiv), Me_2S, Et_2O, rt; (ii) **11** (or **12**), Et_2O, rt, 1 h; (**b**) (i) CuI (2 equiv), isopropenylmagnesium bromide (4 equiv), THF, −78 → −20 °C, 20 min; (ii) **12**, THF, −78 °C → rt, 16 h; (**c**) (i) NaH (2 equiv), THF, rt, 10 min; (ii) MeI (10 equiv), rt, 1–3 d.



Scheme 7. Modified Felkin–Anh attack of cuprate.

in the ^{1}H NMR spectrum of the crude reaction mixture. The entire ring stereochemistry has been confirmed by NOE experiments on related analogues[27] and supports *trans* (*axial*) methylation and is in accordance with the findings of Chounan et al.[24]

In conclusion, we have developed a viable strategy for the formation of chiral, highly substituted cyclohexanone and cyclohexenone derivatives using a tandem conjugate addition/Dieckmann condensation approach where an Evans' chiral auxiliary acts as a leaving group. We are investigating this strategy for the formation of the cyclohexadiene moieties as found in some marine polypropionate metabolites from the *Tridachia* family of molluscs.

Acknowledgements

We wish to thank the Australian Research Council for funding and Flinders University for its support and facilities. We are grateful for the correspondence with R. D. Walkup, and also C. Adams from the A. B. Smith III research group, for their helpful insights with the manipulations of **14** and **15**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.150. Supporting information available. Copies of NMR spectra, experimental procedures and data for compounds **22**–**27**.

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25. All new compounds gave spectroscopic data in agreement with the assigned structures. Compound **25** had $[\alpha]_D^{20}$ −131.9 (*c* 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50–6.46 (m, 1H, C*H*=C), 4.11 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 2.64–2.56 (m, 1H, C*H*(CH_3)CH=C), 2.17 (qd, 1H, J = 7.0, 5.3 Hz, C(CH_3)C*H*(CH_3)), 1.82–1.79 (m, 3H, C(CH_3)=CH), 1.42 (s, 3H, C(CH_3)), 1.22 (t, 3H, 7.1 Hz, OCH_2CH_3), 1.09 (d, 3H, J = 7.0 Hz, C(CH_3)CH-(CH_3)), 1.03 (d, 3H, J = 7.2 Hz, CH(CH_3)CH=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.4, 173.4, 147.6, 133.5, 60.8, 55.6, 41.8, 33.6, 20.3, 16.4, 14.7, 13.9, 13.0; HRMS (LSI) calculated for $C_{13}H_{19}O_3^+$ (M^+−H): 223.1334; found:223.1328. Compound **26** had $[\alpha]_D^{20}$ −96.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37–6.34 (m, 1H, C*H*=C), 2.90–2.79 (m, 1H, C*H*(CH_3)CH=C), 2.24, (s, 3H, CH_3CO), 2.21–2.12 (m, 1H, C(CH_3)C*H*(CH_3)), 1.81 (dd, 3H, J = 2.6, 1.4 Hz, C(CH_3)=CH), 1.35 (s, 3H, C(CH_3)), 1.08 (d, 3H, J = 7.2 Hz, CH(CH_3)CH=C), 0.89 (d, 3H, J = 6.9 Hz, C(CH_3)CH(CH_3)); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.3, 200.0, 147.4, 133.5, 62.0, 42.5, 31.9, 30.8, 21.0, 16.9, 16.0, 11.3; HRMS (EI) calculated for $C_{12}H_{18}O_2$ (M^+):194.1307; found:194.1313. Compound **27** had $[\alpha]_D^{20}$ −69.0 (*c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41–6.39 (m, 1H, C*H*=C), 4.86–4.84 (m, 1H, =CH_ACH_B), 4.72–4.70 (m, 1H, =CH_ACH_B), 3.08–2.97(m, 1H, C*H*(CH_3)CH=C), 2.70 (dd, 1H, J = 5.7, 1.2 Hz, C*H*C(CH_3)=CH_2), 2.19 (s, 3H, CH_3CO), 1.84–

1.82 (m, 3H, C(CH_3)=CH), 1.57–1.56 (m, 3H, C(CH_3)=CH_2), 1.42 (s, 3H, C(CH_3)), 1.08 (d, 3H, J = 7.5 Hz, CH(CH_3)CH=C); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.0, 199.1, 147.4, 143.0, 134.5, 118.4, 61.6, 57.8, 29.7, 29.6, 24.6, 22.6, 17.4, 16.0; HRMS (ESI) calculated for $C_{14}H_{20}O_2Na^+$ (M+Na^+): 243.1361; found: 243.1352.

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