Tetrahedron Letters 49 (2008) 7021–7023

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of the C12–C24 fragment of peloruside A by silyl-tethered diastereomer-discriminating RCM

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ARTICLE INFO

Article history:
Received 21 August 2008
Accepted 22 September 2008
Available online 26 September 2008

Keywords:
Metathesis
Stereoselectivity
Silyl tether
Natural product synthesis

ABSTRACT

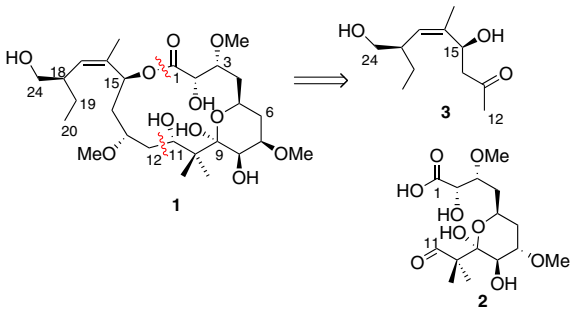
The C12–C24 fragment of peloruside A has been synthesized using, as a key step, a silyl-tethered ring closing metathesis reaction to form the C16–C17 (*Z*)-alkene. The metathesis reaction discriminates between diastereoisomers of the starting material. A diphenylsilyl bis-ether provides simultaneous protection for the C15 and C24 hydroxyl groups, and is expected to lead to high 1,5-*anti* selectivity in subsequent aldol reactions of the methyl ketone, allowing for a convergent stereoselective synthesis of peloruside A.

The isolation of peloruside A from the marine sponge *Mycale hentscheli* was reported in 2000 by Northcote et al.[1] Miller and co-workers established peloruside A to be a potent cytotoxic agent with microtubule stabilizing characteristics similar to those of paclitaxel and docetaxel.[2] Moreover, peloruside A has a microtubule binding site different from that of the taxoid drugs, and has lower susceptibility to the action of drug efflux pumps. When added to cancer cells in combination with taxoid-site drugs, peloruside A displays synergy, which enhances the antimitotic action.[3] These features make it exciting as a pre-clinical drug candidate.

Although Northcote and West were able to determine the relative stereochemistry of peloruside A through extensive NMR studies, the absolute stereochemistry was not revealed until the first total synthesis was completed by De Brabander and co-workers.[4] Since then, total syntheses have been reported by the research groups of Taylor[5] and Ghosh.[6]

Our efforts towards the synthesis of peloruside A (**1**) are based around a convergent strategy, which invokes an aldol coupling of two main fragments: a C1–C11 aldehyde **2** and a C12–C24 methyl ketone **3** (Scheme 1). The synthesis of a protected form of compound **3** using silyl-tethered ring closing metathesis is the subject of this Letter. Alternative fragments of peloruside A related to **3** have been reported by several groups.[7]

Our retrosynthesis of a suitably protected form of the C12–C24 ketone **3**, viz. compound **4** (Scheme 2), is succinct and establishes a convergent synthesis that relies on the one-pot coupling of three components: 2-ethylbut-3-en-1-ol (**6**), (*S*)-β-hydroxyketone (*S*)-**7**,



Scheme 1. Structure and retrosynthetic analysis of peloruside A.

and dichlorodiphenylsilane, to produce diene **5**. Ring closing metathesis (RCM) of this diene is used to access compound **4**. The diphenylsilyl bis-ether of **4** provides simultaneous protection for the C15 and C24 hydroxyl groups, and is integral to our global approach to the synthesis of peloruside A. The structure of compound **4** enables three key strategic advantages:

(1) Compound **4** may be generated by silyl-tethered RCM[8] of diene **5**, which will produce the C16–C17 alkene with the desired (*Z*)-geometry. Silyl-tethered RCM reactions are surrogates for cross-metathesis processes,[8] with the added benefit that they control the geometry of the alkene produced, especially if the ring formed is small- to medium-sized.[8,9]

(2) Observations of kinetic resolution in silyl-tethered RCM reactions, in some cases causing diastereoselectivity,[9,10] indicate an opportunity for stereochemical discrimination in the RCM reaction that forms compound **4**. This would provide control of the

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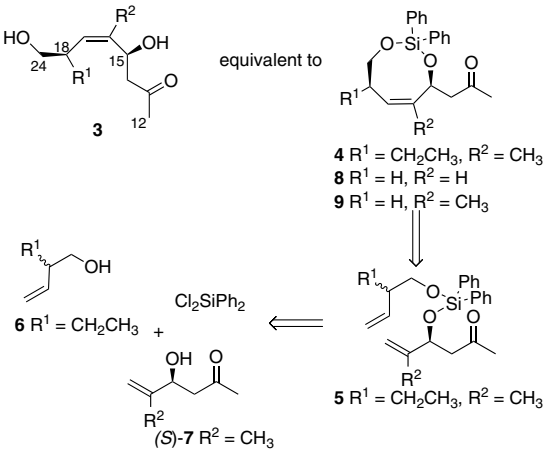
doi:10.1016/j.tetlet.2008.09.133

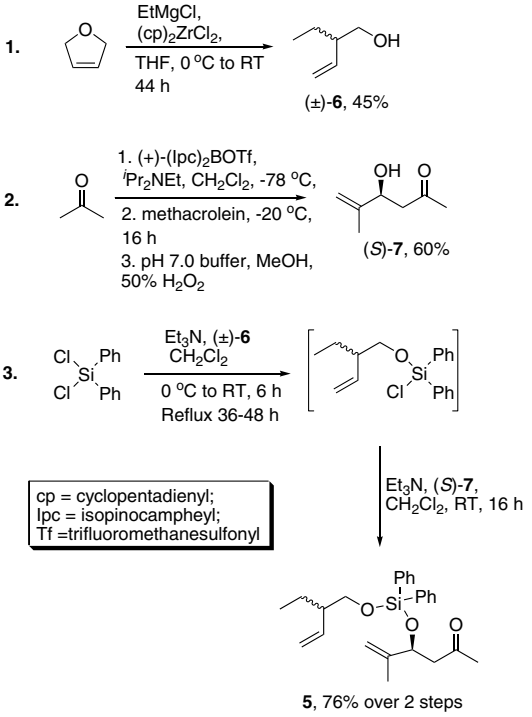


Scheme 2. Retrosynthetic analysis of the C12–C24 fragment.

relative stereochemistry at C15 and C18, delivering the desired product (15*S*,18*R*)-**4**.

(3) Compound **4** should deliver the required 1,5-*anti*-induction[11] during the subsequent aldol reaction with the C1–C11 aldehyde **2**. Indeed, a preliminary study using simplified analogues of the C12–C24 fragment of peloruside A, including **8** and **9** (Scheme 2), gave promising results with high 1,5-*anti*-induction in the subsequent aldol reaction.[12] This model study was performed on dienes lacking the ethyl and/or methyl substituents, and it was anticipated that inclusion of these substituents would be a simple extension of the methodology.

Installation of the ethyl group into the homoallylic alcohol was achieved by treatment of 2,5-dihydrofuran with ethylmagnesium chloride, using zirconocene dichloride (Eq. 1, Scheme 3).[13a] This provided racemic 2-ethylbut-3-en-1-ol [(±)-**6**] in modest yields. Ultimately, it was intended that enantiomerically pure alcohol (*R*)-**6** could be prepared by ethylmagnesation of 2,5-dihydrofuran



Scheme 3. Synthesis of silyl-tethered diene **5**.

catalyzed by (*S*)-ethylene-1,2-bis(η[5]-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride [(EBTHI)$ZrCl_2$].[13b] The enantiomer of this fragment [(*S*)-**6**] was used in De Brabander's synthesis of *ent*-peloruside A.[4] Meanwhile, (*S*)-β-hydroxyketone (*S*)-**7** was prepared by enantioselective boron-mediated aldol reaction of acetone and methacrolein (Eq. 2, Scheme 3).[14]

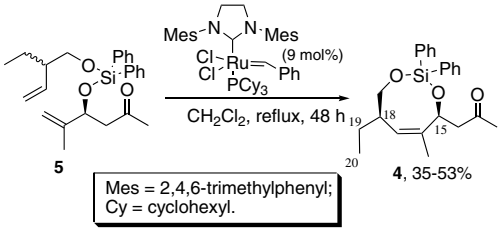
Formation of the diene **5** proceeded smoothly, in a one-pot reaction, by treatment of dichlorodiphenylsilane with homoallylic alcohol (±)-**6** followed, after 48 h, by β-hydroxyketone (*S*)-**7** (Eq. 3, Scheme 3).[15] Due to the use of racemic **6**, it was expected that this reaction would provide two diastereomers. These were indeed evident in the ^{13}C NMR spectrum by doubling of some peaks, but the diastereomers were indistinguishable by ^{1}H NMR spectroscopy.

Ring closing metathesis of the diene **5** proved far more challenging than the equivalent reactions of the des-ethyl variants **8** and **9** previously reported.[12] Indeed, alkenes with alkyl groups in the allylic position are notably sluggish in their engagement in RCM reactions.[16] Attempts were carried out on the mixture of diene diastereoisomers **5** and, after initial tests with different metathesis catalysts, Grubbs' second generation catalyst was selected as the most effective. After exploring an extensive matrix of time, concentration, catalyst quantity, solvent and temperature, conditions were found that provided the required dioxasilocine **4** (Scheme 4). These optimized conditions involved the slow addition (over 24 h) of diene **5** to a dichloromethane solution of 9 mol % catalyst at reflux, followed by heating for a further 24 h.[17]

To our delight, the ^{13}C NMR spectrum of dioxasilocine **4** displayed only one set of peaks, indicating the presence of only one diastereoisomer. Additionally, NOE correlations provided unequivocal evidence for the correct relative stereochemistry as desired for the side chain of peloruside A. In particular, a significant through-space interaction was observed between H15 and H18, which is consistent with (15*S*,18*R*)-stereochemistry, as required in the natural product (Fig. 1). Furthermore, there was no interaction seen between H15 and either H19 or H20. Thus, it appears that a kinetic resolution process occurs during this RCM reaction, such that the required diastereoisomer is fortuitously isolated from the reaction in approximately 35% overall yield, a very reasonable 70% of the theoretical yield for this stereoisomer. The remainder of the material appeared to be recovered starting diene and a product of cross-metathesis.

Related resolution processes had been observed previously in RCM reactions. Indeed, diastereoselectivity has been reported in silyl-tethered RCM reactions forming eight-membered silyl bisethers.[9,10] In addition, Roulland and Ermolenko observed partial dynamic kinetic resolution in RCM reactions of α-alkylated ester diastereomers during their synthesis of the C12–C24 fragment of peloruside A.[7d]

The stereoselectivity obtained in this RCM reaction can be justified by a mechanistic rationale related to that proposed by Evans for the formation of dioxasilocines by diastereoselective silyl-tethered RCM reaction (Fig. 2).[10] The stereochemistry set by C15 and the preference of the substituent at this position to reside in the pseudoequatorial position lead to the observed kinetic resolution of the C18 centre, since diene (15*S*,18*R*)-**5** reacts via a favoured



Scheme 4. Synthesis of dioxasilocine **4** from diene **5** by silyl-tethered RCM.

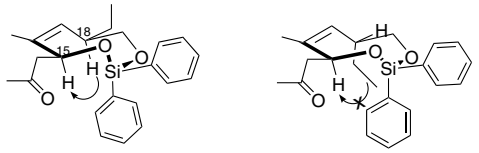


Figure 1. Key NOE correlations used in stereochemical assignment of dioxasilocine **4**.

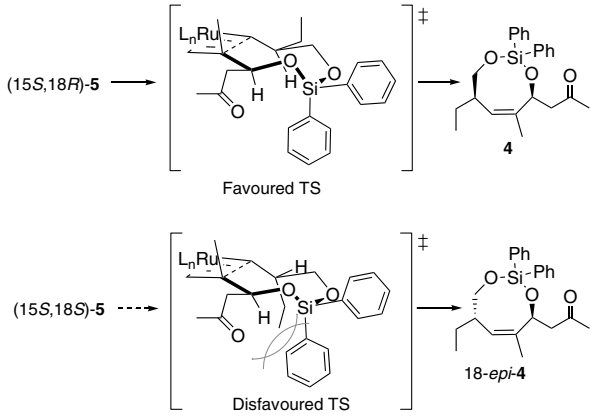


Figure 2. Proposed transition states for silyl-tethered ring closing metathesis reactions of (15*S*,18*R*)-**5** (favoured) and (15*S*,18*S*)-**5** (disfavoured).

transition state, where the ethyl group also resides in the pseudoequatorial position. Conversely, the diastereoisomeric diene (15*S*,18*S*)-**5** must adopt a disfavoured transition state, having steric interactions between the pseudoaxial ethyl group and one of the phenyl rings, and thus reacts more slowly.

In one particular RCM experiment, we found the yield of dioxasilocine **4** to be 53%. This may have been due to loss of fidelity in the stereocontrol of the kinetic resolution, with a small quantity of 18-*epi*-**4** formed through a slow RCM process via the disfavoured transition state. However, this undesired minor product could not be detected by either GC or spectroscopic means. An alternative explanation is that there was a small measure of diastereoselectivity in the formation of the silyl bis-ether **5**, which led to a greater proportion of (15*S*,18*R*)-**5** in the diastereomeric mixture of starting diene. It is anticipated that stereoselective preparation of *R*-**6** for incorporation into diene **5** will lead to the RCM product in high yield; yet the resolution process described above has merit as it proceeds without the requirement for the costly (EBTHI)$ZrCl_2$ catalyst.

In summary, we have completed the synthesis of the C12–C24 fragment of peloruside A in a form suitable for aldol coupling to the C1–C11 portion. Ring closing metathesis using a silyl-tethered diene provided target dioxasilocine **4** with the correct stereochemistry through kinetic resolution of a diastereoisomeric mixture of diene **5**.

Acknowledgements

Financial support from the Foundation for Research, Science and Technology, New Zealand is gratefully acknowledged. We sincerely thank Dr. Bridget Stocker for synthesis advice, and Associate Professor Peter Northcote and Dr. John Ryan for sharing their NMR expertise.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.133.

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15. *Synthesis of compound* **5**: To a solution of dichlorodiphenylsilane (1.2 g, 4.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Et_3N (350 mg, 3.5 mmol) followed by a solution of alcohol (±)-**6** (320 mg, 3.2 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was then warmed to 40 °C and stirred for 48 h. After this time, the reaction mixture was cooled again to 0 °C and Et_3N (1.0 g, 10.0 mmol) was added, followed by β-hydroxyketone (*S*)-**7**[14] (1.0 g, 8.0 mmol) as a solution in CH_2Cl_2 (5 mL). The resulting solution was warmed to rt and was stirred overnight before being quenched with satd aq $NaHCO_3$ (20 mL). The two-phase mixture was then separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic fractions were combined and washed with sat. aq. brine (2 × 20 mL) and water (15 mL), then dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Gradient flash chromatography (20:1–5:1 hexanes/EtOAc) provided diene **5** (980 mg, 76%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.42 (m, 2H), 7.36 (m, 4H), 5.63 (m, 1H), 5.05–5.01 (complex m, 2H), 4.90 (m, 1H), 4.77–4.75 (complex m, 2H), 3.64 (d, *J* = 6.1 Hz, 2H), 2.78 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.55 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.14 (m, 1H), 2.07 (s, 3H), 1.70 (s, 3H), 1.58 (m, 1H), 1.26 (m, 1H), 0.84 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 145.4, 139.96 and 139.92, 135.08 and 135.06, 132.74 and 132.65, 130.28 and 130.23, 127.75 and 127.68, 115.8, 112.28 and 112.27, 73.3, 66.2, 50.3, 47.89 and 47.88, 30.9, 23.5, 17.39 and 17.38, 11.5. IR (neat) 3100–2850, 1715, 1429, 1357, 1162, 1115, 1060, 997, 906, 740, 717, 699 cm^{-1} HRMS (ESI) calcd for $C_{25}H_{32}O_3SiNa^+$ $(M+Na)^+$ 431.2013, found 431.2028.
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17. *Synthesis of compound* **4**: To a solution of Grubbs' second generation catalyst (25 mg, 0.029 mmol) in refluxing CH_2Cl_2 (5 mL) was added diene **5** (120 mg, 0.32 mmol) in CH_2Cl_2 (50 mL) dropwise over 24 h. The refluxing solution was then stirred for a further 24 h before being cooled to rt, and the solvent was removed under reduced pressure. The resulting residue was redissolved in 10:1 hexanes/EtOAc and was filtered through a pad of silica gel. Activated charcoal (50 wt. equiv) was then added, the suspension was stirred for 24 h, then filtered, and the solvent was removed under reduced pressure. Flash chromatography (50:1 hexanes/EtOAc) provided the dioxasilocine **4** (56 mg, 53%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.42–7.34 (complex m, 6H), 5.40 (dd, *J* = 8.9, 4.6 Hz, 1H), 5.06 (dd, *J* = 8.9, 0.9 Hz, 1H), 4.09 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.61 (t, *J* = 10.5 Hz, 1H), 3.06 (dd, *J* = 15.3, 9.1 Hz, 1H), 2.75 (m, 1H), 2.61 (dd, *J* = 15.3, 4.6 Hz, 1H), 2.23 (s, 3H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.35 (m, 1H), 1.20 (m, 1H), 0.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 138.5, 134.7, 134.5, 134.40, 134.35, 134.31, 134.0, 133.5, 130.00, 129.95, 127.9, 127.8, 127.71, 127.65, 69.9, 67.5, 48.2, 42.5, 31.1, 24.7, 19.1, 12.0. IR (neat) 3070–2870, 1716, 1591, 1429, 1122, 739, 716 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{29}O_3Si^+$ $(M+H)^+$ 381.1881, found 381.1862.