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A connective approach to the tetrahydropyran subunit of polycavernoside A via a novel 1,1-dianion equivalent

Carlos Pérez-Balado and István E. Markó*

Université catholique de Louvain, Département de Chimie, Unité de Chimie Organique et Médicinale, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium

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Abstract—Racemic tetrahydropyran **3** was efficiently synthesised from allylsilane **6** and aldehyde **7** via an intramolecular Sakurai cyclisation. In a single step, the relative configuration of three chiral centres was established. Allylsilane **6** was readily assembled from 1-iodo-1-selenopropene **10**, a synthetic equivalent of a propene 1,1-dianion.

Polycavernoside A **1** is the major component of a small family of novel and structurally unique macrolide disaccharides(polycavernosides). Isolated in 1993 by Yasumoto et al. from the red alga *Polycavernosa tsudai*, polycavernoside A was identified as the toxin responsible for the fatal human intoxication that occurred in the island of Guam, in 1991.[1] Since the elucidation of its planar structure, this powerful marine toxin became the target of several synthetic groups, undoubtedly attracted by its challenging architectural and biological features. Polycavernoside A **1** possesses an unusual 13-membered keto-lactone ring and an interesting five-membered hemiketal function adjacent to the ketone group. Moreover, a labile triene moiety is linked to C-15 (Fig. 1). In 1998, Murai and co-workers published the first total synthesis of **1**,[2] establishing at the same time its absolute stereochemistry. Two other total syntheses have been reported to date.[3]

Our retrosynthetic analysis is depicted in Figure 1. Disconnection of the C_1–O and C_9–C_{10} bonds leads to three fragments of approximately the same molecular complexity. The northern subunit consists of the five-membered lactone **4**, bearing the trienyl side chain, and the southern moiety **2** embodies a tetrasubstituted

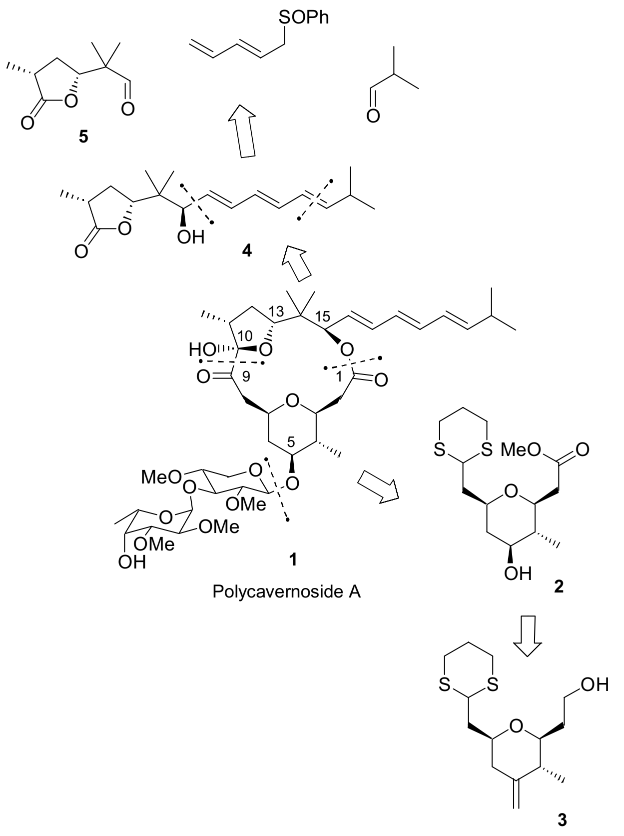

Figure 1.

Keywords: Allylsilanes; Polycavernoside A; 1-Iodo-1-selenoalkenes; Sakurai cyclisation.

* Corresponding author. Tel.: +32 10 47 87 73; fax: +32 10 47 27 88; e-mail: marko@chim.ucl.ac.be

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tetrahydropyran core. The disaccharide residue has already been efficiently prepared by Murai and coworkers.[4] In a previous letter, we have reported an expedient synthesis of **4** from the readily available γ-butyrolactone subunit **5**.[5] As a continuation of our endeavours towards a flexible and versatile construction of **1**, we wish to report a concise and stereocontrolled approach to the tetrahydropyran subunit **2**, utilising an intramolecular Sakurai cyclisation (IMSC) as the key step. This reaction has proved to be a powerful tool for the assembly of tri- and tetrasubstituted tetrahydropyrans, with excellent control of their relative and absolute stereochemistry. This methodology has already been successfully applied in our laboratory to the synthesis of pseudomonic acid B, milbemycin β3 and the middle core of amphidinols.[6]

Following our strategy, the southern subunit **2** could be derived from the tetrahydropyran **3** by a few functional group transformations. Thus, the preparation of ***rac*-3** became our prime objective. Our antithetic analysis of ***rac*-3** is shown in Figure 2. Application of the IMSC retron to ***rac*-3** leads to the generation of two simple fragments: the allylsilane **6** and the protected β-hydroxy aldehyde **7**. The condensation of these two fragments should afford stereoselectively the requisite *exo*-methylene tetrahydropyran ***rac*-3**. The intramolecular Sakurai cyclisation is believed to proceed via a two-step mechanism. The coupling between an allylsilane such as **6** and an aldehyde, in the presence of a Lewis acid, generates initially an oxocarbenium cation intermediate, which undergoes subsequent ring closure by intramolecular nucleophilic addition of the pendant allylsilane function, to give a tetrahydropyran ring possessing an exocyclic C=C bond (Scheme 1). The relative configuration of the three stereogenic centres in the final product is governed by the preference of the substituents to occupy pseudoequatorial positions in the chair-like transition-state during the ring closure step.[7] An important parameter in the control of the relative orientation of the substituents in the final adduct is the geometry of the C=C bond of the allylsilane. According to this model, the *Z*-allylsilane **6** is required to obtain the tetrahydropyran possessing the correct stereochemistry as present in polycavernoside A.

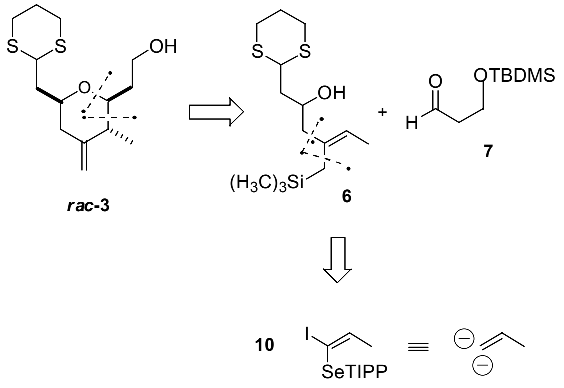
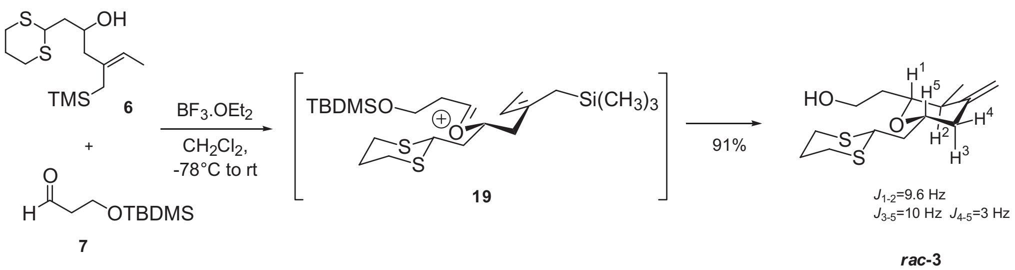


Figure 2.

Despite the number of procedures described in the literature for the synthesis of alkenes, there are few, simple and general methodologies that allow the preparation of trisubstituted allylsilanes with good stereocontrol of the double bond geometry.[8] In order to explore new strategies in this field, we decided to prepare allylsilane **6** from a synthetic equivalent of an alkene 1,1-dianion. Several reports describe the synthesis of alkene 1,1-dianions.[9] Unfortunately, most of these species were found to suffer from serious shortcomings, such as lack of reactivity, difficulty in handling and, often, tedious preparation. In the event, it was found that 1,1-iodoselenoalkene **10** was an interesting and versatile intermediate that could readily be transformed into a variety of di- and tri-substituted olefins. In the preceding letter,[10] we have disclosed some of our preliminary results on the efficient preparation of these 1,1-iodoselenoalkenes. Sequential functionalisation of both heteroatom positions should lead stereoselectively to the desired allysilane **6**.

1-Iodo-1-selenoalkene **10** was prepared in two steps from propyne. Deprotonation of **8** with *n*-BuLi generated the corresponding acetylide, which was subsequently reacted with 2,4,6-triisopropylphenylselenyl bromide, affording the 1-selenoalkyne **9** (87% yield). Hydroalumination of **9** with DIBAL-H led to the quantitative formation of a (*Z*)-1,1-alumino-selenoalkene intermediate, which was quenched with I_2 under carefully controlled conditions to give selectively, and with retention of configuration of the C=C bond, the 1,1-iodo-selenoalkene **10** in 92% yield. The use of the sterically hindered 2,4,6-triisopropylphenyl (TIPP) group on selenium proved mandatory to prevent the competitive (sp)C–Se bond cleavage during the hydroalumination step.[10]

Opening of the dithianylmethyl oxirane **11** by the vinylic anion derived from **10**, by I/Li exchange with *n*-BuLi, in the presence of $BF_3{\cdot}OEt_2$, resulted in the formation of



Scheme 1.

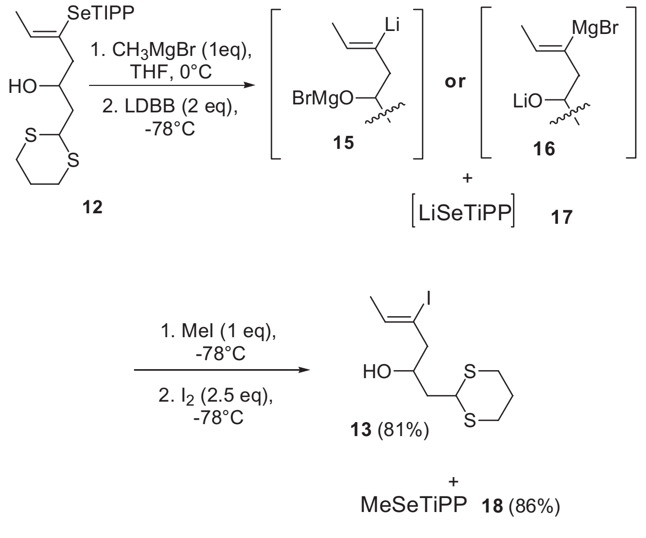
the homoallylic alcohol **12** in 50% yield based upon **10** (100% based upon oxirane **11**). In the absence of a Lewis acid, this vinyl lithium species proved to be rather unreactive towards oxirane **11**. The moderate yield in the presence of $BF_3{\cdot}OEt_2$ is due to the concomitant formation of an unreactive vinyl fluoroborate intermediate,[11] which consumes 50% of the vinyl lithium reagent. By employing 2 equiv of vinylselenide **10**, a quantitative yield of adduct **12** could be reached.

After treatment of **12** with methylmagnesium bromide, in order to deprotonate the homoallylic hydroxy function, the alkenyl C–Se bond was reductively cleaved with LDBB (lithium 4,4′-di-*t*-butylbiphenylide),[12] generating the carbanion **15** and lithium selenoate **17** (Scheme 2). Whilst it is reasonable to assume that the lithium salt **15** is initially formed under these reductive conditions, it is quite plausible that metal exchange might take place under the reaction conditions, leading either to **16** or an equilibrating mixture of **15** and **16**, with the latter reagent being the active species in the subsequent coupling step. In this regard, using *n*-BuLi to perform the deprotonation of alcohol **12**, followed by LDDB treatment, led to significant erosion in the yields of **13**. Attempts to react these organometallic derivatives with various alkylating agents, in order to introduce the CH_2TMS moiety, failed probably owing to the lack of reactivity of these silyl-containing electrophiles. Quenching of the intermediates **15**/**16** with I_2 led to the vinyl iodide **13** in excellent yield.[13] Cross-coupling of **13** with trimethylsilylmethyl magnesium chloride, catalysed by $Pd(PPh_3)_4$, ultimately generated the requisite allylsilane **6** in 55% overall yield from **12**. It is noteworthy that 1 equiv of MeI had to be added to the lithiated species **15**/**16**, before the iodine quench, in order to obtain good yields of **13**. In this case, MeI rapidly and chemoselectively traps the lithium selenoate **17**, generated during the reductive cleavage of vinyl selenide **12**. In the absence of MeI, **17** reacts competitively with I_2, leading to the formation of numerous, undesired products. The *Z* configuration of the C=C bond of the allylsilane **6** was established by NOE experiments and subsequently confirmed by the analysis of the coupling constants in adduct ***rac*-3** (Scheme 3), indicating that the transformation of **10** to **6** took place with retention of configuration.

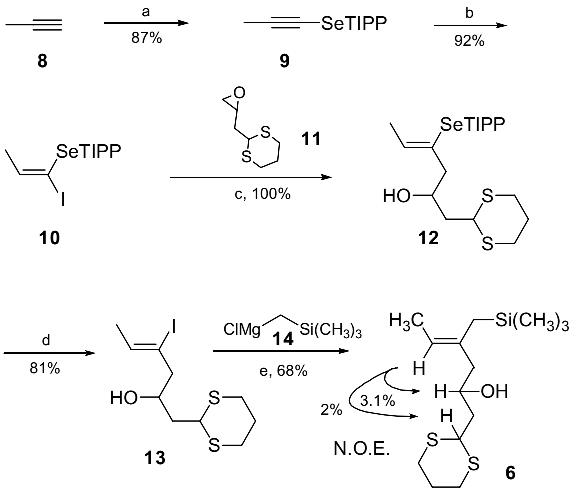
With a ready supply of allylsilane **6** in hand, we next turned our attention to the crucial intramolecular Sakurai cyclisation. We were delighted to observe that the tetrahydropyran ***rac*-3** was readily obtained, in 91% yield, when **6** and aldehyde **7** were treated with 1 equiv of $BF_3{\cdot}OEt_2$, at low temperature. Interestingly, we found that a smooth deprotection of the TBDMS group occurred when the reaction mixture was allowed to warm up to room temperature, affording in a single operation, the free alcohol.[14] The relative stereochemistry of ***rac*-3** was unambiguously established by careful analysis of its ^1H NMR spectrum. The coupling constant values of 9.6 and 10 Hz for the H^1–H^2 and H^5–H^3 hydrogen pairs clearly indicate that the three substituents occupy equatorial positions on the tetrahydropyran ring system (Scheme 1).

The relative stereochemistry of adduct ***rac*-3** can be easily rationalised by examining the transition state invoked in the final cyclisation of the allylsilane residue onto the oxocarbenium cation **19**. In order to minimise steric interactions, the substituents occupy pseudoequatorial positions. The geometry of the allylsilane double bond controls the C_2 configuration.

In summary, we have shown that racemic tetrahydropyran **3** could be synthesised efficiently from allylsilane **6** and aldehyde **7** using the IMSC condensation as a key step. By the judicious control of the allylsilane C=C double bond, the relative stereochemistry of three chiral centres could be established in a single operation. We have also demonstrated that 1-iodo-1-selenoalkenes are useful precursors for the synthesis of stereodefined trisubstituted allylsilanes. These interesting vinylselenides can be considered as alkene-1,1-dianion



Scheme 2.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, THF, −40 °C then 2,4,6-triisopropylphenylselenyl bromide, C_6H_6, 0 °C to rt, 5 h; (b) DIBAL-H, hexane, 0 °C to rt, 3 h, then I_2, THF, −78 °C to rt, 2 h; (c) *n*-BuLi, THF, −78 °C, 30 min, $BF_3{\cdot}OEt_2$, then (±)-**11**, THF, −78 °C, 1 h; (d) CH_3MgBr, THF, 0 °C, 15 min, LDBB, −78 °C, 30 min, MeI, −78 °C, 15 min, then I_2, −78 °C, 1 h; (e) **14**, $Pd(PPh_3)_4$, THF, rt, 9 h.

equivalents. Current efforts are now being directed towards delineating the scope and applications of selenoalkenes such as **10**, establishing an enantioselective synthesis of tetrahydropyran **3** and completing the total synthesis of polycavernoside A. The results of these investigations will be reported in due course.

Acknowledgements

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13. *Experimental procedure for the preparation of vinyl iodide* **13**: To a solution of selenide **12** (130 mg, 0.26 mmol) in THF at 0 °C and under argon, was added dropwise CH_3MgBr (130 μL, 0.39 mmol and 3.0 M in Et_2O). After stirring for 15 min at 0 °C, this solution was added, via syringe, to a LDBB solution (2.5 mL, 0.3 M in THF) maintained at −78 °C. At the end of the addition, the solution colour changed from dark green to clear red. The mixture was stirred for 30 min at −78 °C and neat MeI (16 μL, 0.26 mmol) was added. Stirring was continued for another 10 min. The solution became colourless. A solution of I_2 (165 mg, 0.65 mmol) in THF (2 mL) was added dropwise and the mixture stirred for 1 h at −78 °C. The reaction was quenched by addition of ethanol (2 mL) at −78 °C and the solution was allowed to reach room temperature. It was diluted with petroleum ether (5 mL), washed with a satd aq solution of $Na_2S_2O_3$ (5 mL) and extracted several times with petroleum ether. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O, 1/1) to afford 73 mg (81% yield) of the title compound as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ_H (ppm): 5.73 (1H, qt, $J = 6.3$, 1.1 Hz), 4.28 (1H, dd, $J = 8.4$, 6.0 Hz), 4.35–4.20 (1H, m), 2.99–2.80 (4H, m), 2.62 (2H, d, $J = 6.5$ Hz), 2.25–1.80 (4H, m), 1.77 (3H, d, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm): 128.4, 106.3, 67.3, 53.3, 44.7, 42.4, 30.6, 30.2, 26.4, 22.5. IR (neat): 3348, 2938, 2900, 1647, 1422, 1243, 1115 cm^{-1}. MS (EI) *m/z* (%): 219 [M^+–I] (15), 205 (29), 188 (22).
14. *Experimental procedure for the preparation of tetrahydropyran* ***rac*-3**: To a solution of allylsilane **6** (65 mg, 0.21 mmol) and aldehyde **7** (60 μL, 0.32 mmol) in CH_2Cl_2 (2 mL) at −78 °C, under argon, was added $BF_3{\cdot}OEt_2$ (41 μL, 0.32 mmol) dropwise. The reaction mixture was allowed to warm slowly to −30 °C, and the disappearance of the starting material was monitored by TLC. After completion of the reaction, the solution was allowed to reach rt, poured over a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude material was purified by chromatography on silica gel (petroleum ether/Et_2O, 2/1) affording 55 mg (91% yield) of the title compound as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ_H (ppm): 4.80 (1H, d, $J = 1.5$ Hz), 4.73 (1H, d, $J = 1.5$ Hz), 4.23 (1H, dd, $J =$ 9.3, 4.8 Hz), 3.92–3.82 (2H, m), 3.62 (1H, tt, $J = 10$, 3 Hz), 3.18 (1H, td, $J = 9.6$, 3 Hz), 3.00–2.66 (4H, m), 2.30–1.60 (9H, m), 1.99 (3H, d, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C (ppm): 148.3, 107.3, 83.2, 75.2, 60.9, 44.4, 42.5, 41.5, 41.4, 35.6, 30.8, 30.5, 26.1, 12.7. IR (neat): 3332, 3046, 2935, 2899, 1647, 1423, 1056, 1027. MS (EI) *m/z* (%): 288 [M^+] (89), 214 (34), 145 (78). Anal. Calcd for $C_{14}H_{24}O_2S_2$: C, 58.29; H, 8.39. Found C, 57.54; H, 8.35.