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A new synthesis of the 2,2,3,5,6,6-substituted tetrahydropyran aplysiapyranoid A and its 5-epimer

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Abstract—The vanadium(V)-catalyzed oxidation of bromide in the presence of methyl (*E*)-2-(1-hydroxy-1-methylethyl)-5-phenyl-4-hexenoate furnished 5,6-*trans*-5-bromo-6-phenyl-2,2,6-trimethyl-3-methyloxycarbonyltetrahydropyran, which was converted into the marine natural product aplysiapyranoid A and its 5-epimer, via a short sequence of decarboxylative bromination and transition metal-based procedures for transforming a phenyl into a chlorovinyl substituent.

Aplysiapyranoids A–D are monoterpene-derived secondary metabolites, which have been isolated from the midgut gland of the sea hare *Aplysia kurodai*.[1,2] Due to their cytotoxic profile towards several human tumor cell lines, in association with their restricted availability from natural sources, aplysiapyranoids have become attractive targets in organic synthesis.[3–5] In order to provide adequate quantities of these compounds for succeeding biological experiments it was desired to develop a new synthesis, which was based on a catalytic procedure for constructing the bromofunctionalized tetrahydropyran nucleus from a suitable bishomoallylic alcohol. Further, it was considered useful to design an approach that would allow an application of polar *and* free radical reactions for subsequent functional group interconversions in order to establish a straightforward access to a wider range of analogues of heterocycle **1** in future investigations. In regard of these prerequisites, styrene derivative **2** was chosen as substrate for a new synthesis of aplysiapyranoid A (**1**) and its 5-epimer *epi*-**1** (Fig. 1).[†,‡] A phenyl substituent is known to exhibit a comparatively strong polar effect in electrophilic bromination reactions of olefins and thus was thought to significantly favor a 6-*endo*-selective ring closure reaction in the initial step.[6] Introduction of the second bromo substituent into the heterocyclic core was expected to be feasible via a decarboxylative free radical bromination.[7] A subsequent oxidative degradation of the phenyl into a carbonyl functionality[8] then would provide an appropriate starting point for constructing the (*E*)-configured chlorovinyl substituent of target compounds **1** and *epi*-**1**.

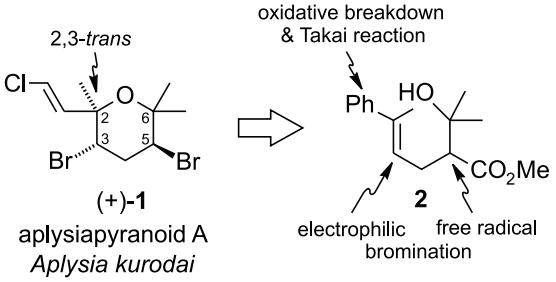

Figure 1. Concept for the construction of aplysiapyranoid A (+)-(**1**).

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† Satisfactory analytical data were obtained for all new compounds prepared in this study. The present communication reports on a proof of concept. Therefore it has been restricted to the synthesis of racemic aplysiapyranoid A (**1**) and *epi*-**1**.

‡ Methyl (*E*)-2-(1-hydroxy-1-methylethyl)-5-phenyl-4-hexenoate (**2**) was prepared by esterification of 4-benzoyl butyric acid (CH_3OH, $CHCl_3$, TsOH, 61°C), selective methylation (CH_3MgI, Et_2O, 20°C), treatment of this crude product with TsOH in a mixture of C_6H_6 and CH_3OH (oil bath: 95°C), and subsequent α-alkylation (LDA, THF, −78°C, then acetone): ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.29$ (2 s, 6H), 2.03 (s, 3H), 2.30–2.44 (br. s, 1H), 2.43–2.77 (m, 2H), 2.55 (m_c, 1H), 3.68 (s, 3H), 5.67 (tq, $J = 6.7$ Hz, $J = 1.5$ Hz, 1H), 7.21–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 16.0$, 26.8, 27.0, 29.2, 51.6, 55.7, 71.0, 124.8, 125.7, 126.8, 128.2, 137.0, 143.8, 176.1. $C_{16}H_{22}O_3$ (262.34): calcd C, 73.25; H, 8.45; found: C, 73.72; H, 8.33.

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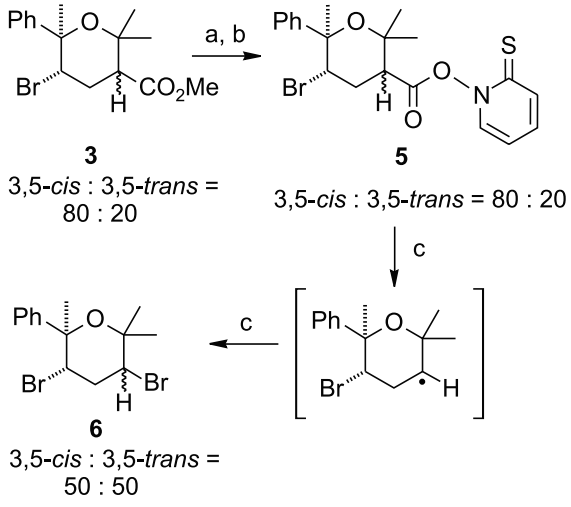
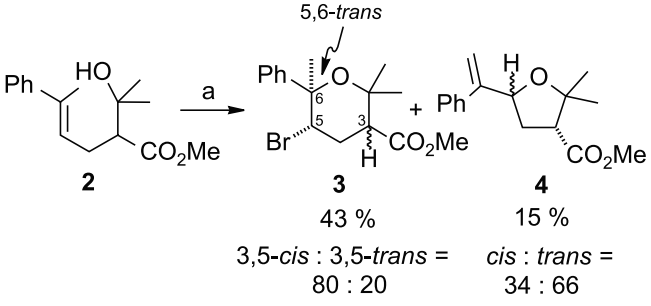
Thus, methyl (*E*)-2-(1-hydroxy-1-methylethyl)-5-phenyl-4-hexenoate (**2**)‡ was treated on a 15 g scale with *tert*-butyl hydroperoxide (TBHP), pyridinium hydrobromide and 5 mol% of catalyst VOL(OEt)(EtOH) [L = *N*-(2-hydroxyphenyl)salicylidenimine dianion][9,10] to furnish 43% of 6-*endo*-bromocyclized product **3** (3,5-*cis*:3,5-*trans* = 80:20) besides 15% of tetrahydrofuran **4** (*cis*:*trans* = 34:66, Scheme 1).[11] Substituents at C5 and C6 in both diastereomers of **3** exhibited relative *trans*-configuration. Formation of 5-(1-phenyl-1-hydroxy-1-ethyl)-substituted tetrahydrofurans or the corresponding tetrahydropyranols as side products, which might have originated from a competing direct vanadium(V)-catalyzed oxygenation of substrate **2**, was not observed.[11] It is worth mentioning that treatment of a solution of alkenol **2** in CH_2Cl_2 (20°C or 40°C) with the standard reagent for conducting 6-*endo*-selective ring closure reactions, i.e. 2,4,4,6-tetrabromocyclohexadienone,[3–5,12,13] provided 5,6-*trans*-configured tetrahydropyran **3** in yields that remained below 20%. Surprisingly, the diastereoselectivity for a likewise obtained product **3** with regard to substitution at C3 and C5 was reversed (3,5-*cis*:3,5-*trans* = 26:74, not shown in Scheme 1).

Saponification of methyl ester **3** using LiOH in aqueous dimethoxyethane (DME) furnished upon neutralization the corresponding carboxylic acid (3,5-*cis*:3,5-*trans* = 80:20, 93%, not shown in Scheme 2). Treatment of the latter compound with *N*-hydroxypyridine-2(1*H*)thione (PTOH) and diisopropylcarbodiimide (DIC) provided mixed anhydride **5** (Scheme 2).[7] Photolysis of alkyl radical precursor **5** in the presence of $BrCCl_3$ led to the formation of dibromide **6** (3,5-*cis*:3,5-*trans* = 50:50, 52% starting from the carboxylic acid derivative of **3**).

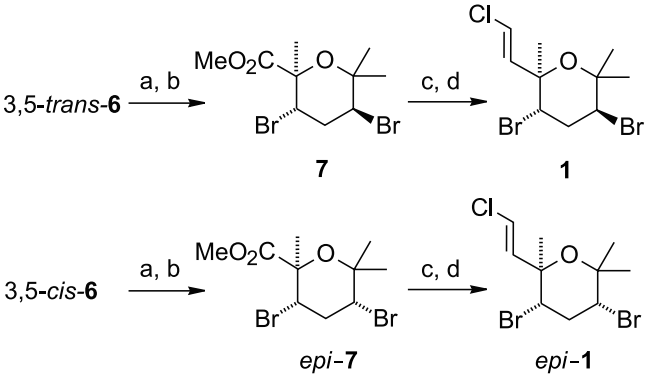
For completion of both syntheses, separated dibromides 3,5-*trans*-**6** and 3,5-*cis*-**6** were treated with the reagent combination of $RuCl_3$ and $NaIO_4$ in order to transform in both instances the phenyl substituent into a carboxyl group (Scheme 3). Since this procedure had originally been developed for preparing carboxylic acids from less functionalized aromatic hydrocarbons,[8] we were pleased to notice that it was also suitable for a chemoselective transformation of both diastereomers of **6**. However, it should be added that the conversion of starting material **6** ceased at some point. It was not possible to resume its oxidation by adding further $RuCl_3$ or supplementary $NaIO_4$ to the reaction mixture. Since separation of likewise prepared carboxylic acids from unreacted substrate **6** at that stage of the synthesis was tedious and associated with loss of substantial amounts of oxidation product, the crude material was treated with MeOH and DIC to provide esters **7** and *epi*-**7**, which were purified by chromatography (Scheme 3). Reduction of the ester functionality in **7** and *epi*-**7** using DIBAH in hexanes/CH_2Cl_2 afforded the corresponding aldehydes. Treatment of these products with $CrCl_2$ and $CHCl_3$ furnished target compounds **1** and



Scheme 2. Formation of 3,5-dibromo-2,2,6,6-substituted tetrahydropyran **6** from heterocyclic ester **3**. *Reagents and conditions*: (a) LiOH, DME, H_2O, 20°C (93%); (b) PTOH, DIC, CH_2Cl_2; (c) $BrCCl_3$, C_6H_6, *hv*, 20°C (52% for steps b and c).



Scheme 1. Application of the vanadium(V)-catalyzed oxidation of bromide in the 6-*endo*-selective bromocyclization of styrene-derived alcohol **2**. *Reagents and conditions*: (a) TBHP (1.1 equiv.), $C_5H_5N{\cdot}HBr$ (1.5 equiv.), VOL(OEt)(EtOH) [5 mol%, L = *N*-(2-hydroxyphenyl)salicylidenimine dianion)],[9,10] CH_3CN, 20°C.



Scheme 3. Completion of the synthesis of aplysiapyranoid A (**1**) and *epi*-**1**, both as racemates. *Reagents and conditions*: (a) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 20°C; (b) CH_3OH, DIC, CH_2Cl_2 (36% for 3,5-*trans*-**6**→**7**, 46% for 3,5-*cis*-**6**→*epi*-**7**); (c) DIBAH in hexanes, CH_2Cl_2, −78°C; (d) $CrCl_2$, $CHCl_3$, THF, 61°C (33% for **7**→**1**, 22% for *epi*-**7**→*epi*-**1**).

epi-**1**.[§,14] The sample of aplysiapyranoid A (**1**) was contaminated with a minor amount of its dechlorinated derivative (4%) and 10% of starting aldehyde, which could be separated from **1** by column chromatography. The final step from the synthesis of *epi*-**1** was not associated with similar complications.

The observation that only moderate yields were attainable from optimized synthetic procedures, which are outlined in Scheme 3, was unexpected and deserves a comment. This fact had been noted for the chloroethenylation step in the synthesis of (+)-**1** in an earlier report.[3] According to our experience, this issue has to be associated with the significant steric crowding in 2,2,3,5,6,6-substituted tetrahydropyrans that sometimes rendered seemingly elementary reactions into troublesome processes.

In summary, we have devised a new synthesis of aplysiapyranoid A (**1**) and its isomer *epi*-**1**, both as racemates. The selected strategy supplements the existing approach.[3] It offers potential for future syntheses of new aplysiapyranoid derivatives, since it takes profit from a transition metal-catalyzed oxidation in the bromine cyclization step and enables the preparation of related compounds under mild and neutral conditions using radical-based transformations.

Acknowledgements

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[§] **1**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.38$ (s, 3H), 1.43 (s, 6H), 2.61–2.68 (m, 2H), 4.39 (dd, $J = 7.8$, 5.0 Hz, 1H, CHBr), 4.47 (dd, $J = 6.2$, 4.0 Hz, 1H, CHBr), 6.14 (d, $J = 13.8$ Hz, 1H), 6.18 (d, $J = 13.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 27.3$, 28.7, 29.0, 37.3, 54.6, 55.1, 75.8, 76.0, 118.4, 138.4. *epi*-**1**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.36$ (s, 3H), 1.47 (s, 3H), 1.53 (s, 3H), 2.59–2.70 (m, 2H), 3.87 (m_c, 2H, 2 CHBr), 6.09 (d, $J = 13.1$ Hz, 1H), 6.29 (d, $J = 13.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 22.1$, 23.3, 30.4, 38.3, 52.8, 53.9, 76.8, 77.1, 119.9, 137.8.