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Development of an approach to the synthesis of the plakortones

M. F. Semmelhack* and Ponnusamy Shanmugam†

Department of Chemistry, Princeton University, Princeton, NJ 08544, USA

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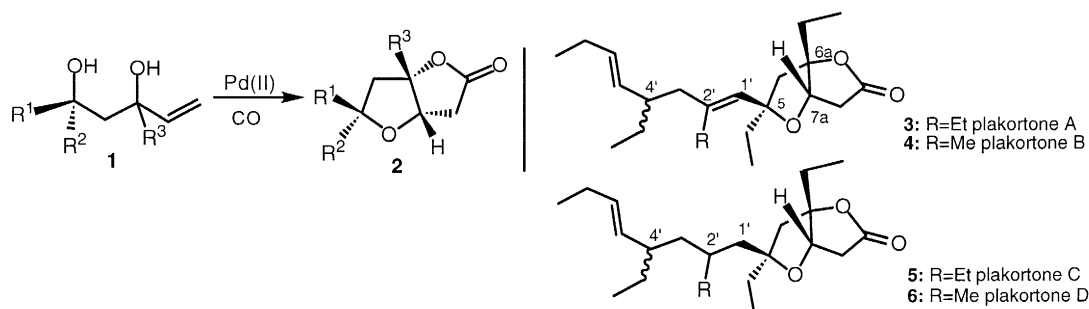
Abstract

A general synthesis of the plakortones has been developed by the synthesis of two key sections, with a focus on Pd(II)-promoted preparation of a *cis*-fused tetrahydrofuranolactone. The key intermediates were obtained in homochiral form starting from asymmetric epoxidation of an allylic alcohol. © 2000 Elsevier Science Ltd. All rights reserved.

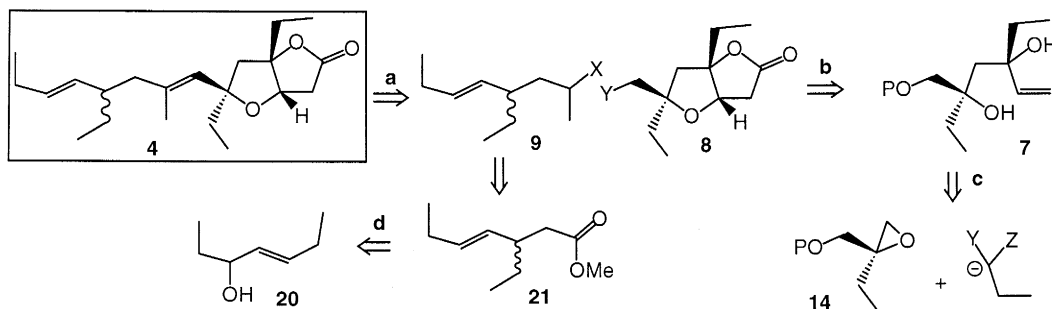
Palladium-promoted intramolecular alkoxycarbonylation of hydroxyalkenes (**1**) has been developed as a route to bicyclic tetrahydrofuran lactones (**2**).^{1–5} The general process was first demonstrated in the construction of a cyclohexane ring with *cis* fused lactone⁶ and later developed to control the relative configuration of the 2,5-substituents around a tetrahydrofuran ring.⁷ Several families of natural products incorporate this ring system and it is an interesting question whether the palladium methodology offers efficient strategies for their construction. The plakortones (**3–6**) were identified in 1996 and show activity as activators of the cardiac sarcoplasmic reticulum Ca⁺²-pumping ATPase and are of potential interest as agents to increase calcium pumping in order to correct cardiac muscle relaxation abnormalities.⁸ The structure is based on detailed ¹H NMR studies and the configuration at C-4' in **3–6** is not defined, and likewise for the configuration at C-2' in **5** and **6**. A few other diverse structures show similar activity (e.g., gingerol⁹ for activation of cardiac SR Ca⁺²-ATPase and plakorin¹⁰ for skeletal muscle Ca⁺²-ATPase), but no detailed SAR work has been published.

* Corresponding author. Tel: +1 609 258-5501; fax: +1 609 258-3409; e-mail: mfshack@princeton.edu (M. F. Semmelhack)

† On deputation from Regional Research Laboratory (CSIR), Trivandrum-695019, India.

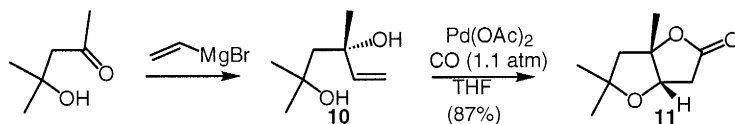


Retrosynthetic analysis: We are prompted by a recent paper¹¹ with similar ideas to report here our progress in developing an approach to the plakortone structures. Key to the palladium methodology, a retrosynthetic analysis is shown in Scheme 1. The key transforms are the alkene coupling (**a**; for plakortones A and B; alternative C–C single bond couplings would be appropriate for plakortones C and D), the palladium alkoxy carbonylation (**b**), the addition of a carbonyl anion equivalent to a homochiral epoxide (**c**), and the enolate Claisen rearrangement (**d**). This analysis results in a short sequence, but exposes obvious selectivity issues in the trisubstituted double bond preparation (**a**) and in creating the second stereogenic center in intermediate **7**. We report here the synthesis of homochiral lactone **8** ($Y=CH_2OH$) and the sulfone, **9** ($X=SO_2Ph$).



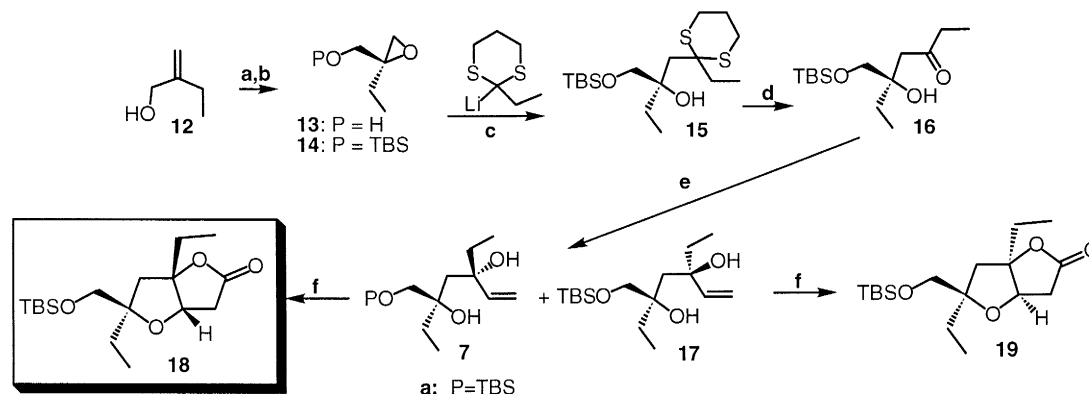
Scheme 1.

The general conversion of **1** to **2** ($R_2, R_3=H$) has ample precedent,¹² but the precursor **7** has two quaternary centers, and the influence of such steric crowding was not previously tested. The simple model **10**, prepared from diacetone alcohol (2.5 mol equiv. of vinyl-MgBr; 71% yield) underwent the desired conversion to give **11** in 87% yield. The Pd(II) was used here in small excess (1.5 mol equiv.) which was convenient on this research scale, although procedures with catalytic Pd(II) and excess Cu(II) as reoxidant are available.^{2,3,11} The formation of the *cis*-fused lactone is general with this methodology. Molecular mechanics analysis¹³ suggests that the *cis* arrangement (**11**) is more stable than the *trans* by 10–15 kcal/mol.



Preparation of the bicyclic lactone: The synthesis of precursor **7** ($P=t$ -butyldimethylsilyl, TBS) is shown in Scheme 2. Following a known procedure,¹⁴ asymmetric epoxidation of the allylic alcohol **12** gave **13** in 97% yield and 85–90% *ee*; protection as the TBS ether (**14**, 86%) followed by displacement with 2-ethyl-2-lithio-1,3-dithiane produced the hydroxy thioketal **15** (98%). The standard hydrolysis¹⁵ affords the β -hydroxyketone **16** in 96% yield. The simplest procedure for preparation of **7a** is by

addition of a vinyl organometallic nucleophile. However, the use of vinylmagnesium bromide led to >80% enolization rather than addition. Several variations were tested; the most effective was to treat **16** with anhydrous CeCl_3 prior to addition of vinylmagnesium bromide.¹⁶



Scheme 2. (a) See Ref. 13a, b; (b) see Ref. 13c; (c) anion prepared from $n\text{BuLi}$ (1.15 mol equiv.) and 2-ethyl-1,3-dithiane (1 mol equiv.) in ether at 0°C , 1 h; then **14** (1 mol equiv. in THF), $0^\circ\text{C}/5$ h and $23^\circ\text{C}/12$ h; (d) yellow HgO (2.2 mol equiv.), HgCl_2 (3 mol equiv.), MeOH , reflux, 18 h; (e) (i) mix CeCl_3 (freshly dried, 1.1 mol equiv.), THF, vinyl-MgBr (2.5 mol equiv., 1 M in THF), -78°C ; (ii) add **16** (1 mol equiv.) in THF, -78°C ; (iii) 0°C , 45 min; (iv) HOAc at -40°C ; (f) see text and Ref. 16

The product mixture had three components: unreacted **16** attributed to enolization (20%), and a mixture of diastereomeric diols, **7a** and **17** (67% together after flash chromatography). ^1H NMR spectral analysis of the mixture indicated a ratio of 4:1 (using the signals due to the methine proton appearing at δ 6.8 and 6.9 ppm). Slow elution of the mixture through a silica gel column afforded the pure diol **7a** (40%) along with a mixture of **7a** and **17** (2.5:1 ratio, 25%). Cyclization¹⁷ of **7a** with $\text{Pd}(\text{OAc})_2$ (2 mol equiv.) in the presence of CO (1.1 atm) in THF at 23°C gave a single bicyclic lactone (**18**) in 86% yield after column chromatography. While **17** could not be obtained in pure form, a mixture (2.5:1) of **7a** and **17** produced a mixture of lactones, again inseparable, but whose ^1H NMR spectral data were consistent with a mixture of **18** and **19**. The relative configurations of **18** were established to be the same as the natural product by thorough NOE-difference studies (examples in Fig. 1 and Table 1).

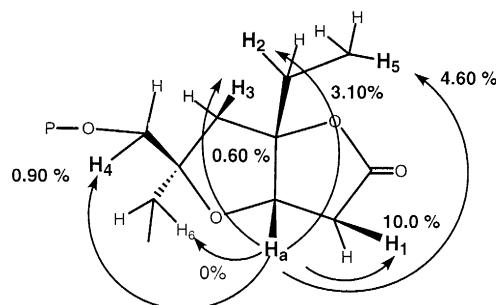


Fig. 1. NOE enhancements with irradiation at H_a (δ 4.52) (500 MHz)

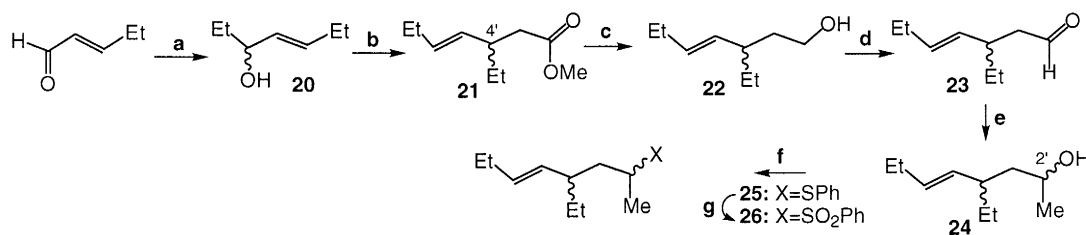
Synthesis of the side chain precursor, 9: The side chain unit is available in racemic form according to Scheme 3, a process which should be readily adaptable to asymmetric synthesis through kinetic resolution of the early intermediate, **20**. Since the configuration of the stereogenic center in the side chain is not established in the plakortones, it will be important to have access to both enantiomers of **20**. Addition of EtMgBr to *E*-2-pentenal¹⁸ gave **20** in 71% yield after fractional distillation. Based on the Johnson protocol¹⁹ for the enolate Claisen rearrangement, an optimized procedure for converting **20** to **21** was

Table 1
Comparison of the chemical shifts and NOE enhancements for bicyclic lactone **18** and the bicyclic lactone portion of plakortone B^{8a}

Proton ^a	18	Plakortone B
H ₁	2.65 (10.0%)	2.66 (+)
H ₂	1.79 (3.1%)	1.76 (+)
H ₃	2.23 (0.60%)	2.30 (+)
H ₄	3.56 (0.90%)	(b)
H ₅	1.00 (4.6%)	0.98 (+)
H ₆	1.71 (0%)	1.70 (0)

(a) in CDCl₃. (b) vinyl proton in the natural product

developed. A mixture of **20**, trimethyl orthoacetate (5 mol equiv.), and propionic acid (0.12 mol equiv.) was heated at 85°C while MeOH distilled through a short fractionating column. When the MeOH ceased to distill (ca. 2 h), the solution was transferred to a sealed tube and heated at 145°C for 24 h. Isolation²⁰ gave **21** as a mixture with the corresponding *Z* isomer (78% yield together; 85:15 based on integration of the vinyl signals in the ¹H NMR spectrum). Reduction of the mixture with LiAlH₄ gave the alcohol **22**, which, after column chromatography, was isolated as a single geometrical isomer (92% yield based on the amount of **21** in the starting *E/Z* mixture). PCC oxidation²¹ gave the aldehyde **23** (76% yield). Addition of MeMgBr led to the diastereomers represented by **24** (3:2 ratio, estimated by ¹H NMR; 95% yield).



Scheme 3. Synthesis of the side chain unit. (a) EtMgBr (1 M in THF, 1.2 mol equiv.), 23°C; (b) see text; (c) LiAlH₄ (2 mol equiv.), ether, 0→23°C, 14 h; (d) pyridinium chlorochromate (1.4 mol equiv.), CH₂Cl₂, 23°C, 1.5 h; (e) MeMgBr (1 M sol. in THF, 1.2 mol equiv., 0°C, 1.5 h); (f) PhSSPh (1.8 mol equiv.), pyridine (ca. 2 mol equiv.), (*n*Bu)₃P (1.5 mol equiv.), 23°C, 5.5 h; (g) PhSeSePh (0.9 mol equiv.), CH₂Cl₂:Et₂O (1:7), 30% H₂O₂ (30 mol equiv.), 0°C, 1 h

Anticipating a Julia coupling²² to join the side chain to the furanolactone, the corresponding phenyl thioether (**25**, 83% yield) and phenyl sulfone (**26**, 95% yield) were prepared by standard procedures.²³ This work provides effective methodology for the formation of the non-racemic furanolactone portion and a method for the side chain synthesis which should be readily adaptable to the preparation of each enantiomer separately. The completion of an asymmetric synthesis of plakortone B is underway.

Acknowledgements

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17. Into a 50 mL 3-necked flask equipped with a rubber septum, stir bar, and 3-way stopcock bearing a balloon was weighed palladium(II) acetate (0.267 gm, 1.18 mmol). The flask was evacuated (0.1 torr) and the flask and balloon were filled with argon. This process was repeated three times with argon. It was then repeated with carbon monoxide (CO) three times. With the balloon filled with CO (ca. 1.1 atm), dry THF (5 mL) was added via syringe followed by a addition over 2 min of a solution of the diol **7a** (0.180 g, 0.593 mmol) in 3 mL of dry THF. The mixture was stirred at 23°C for 4 h and then filtered through a Celite pad. Concentration under reduced pressure followed by silica gel column chromatography using hexane:ethyl acetate (5:1) furnished pure cyclized compound **18** (0.168 g, 86%) as a colorless viscous liquid. R_f : 0.3 (SiO₂, hexane:EtOAc 5:1). ¹H NMR (500 MHz, CDCl₃): δ 4.5 (t, J=2.5 Hz, 1H), 3.5 (d, J=10.5 Hz, 1H), 3.4 (d, J=10.5 Hz, 1H), 2.6 (br s, 2H), 2.2 (abq, J=14 Hz, 2H), 1.8 (approx quintet, J=7 Hz, 1H), 1.7 (approx quintet, J=7 Hz, 1H), 1.55 (m, 2H; br q), 1.0 (t, J=7.5 Hz, 3H), 0.9 (s overlapping t, 12H), 0.06 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 176.4, 99.2, 88.4, 83.2, 70.3, 41.7, 38.8, 30.3, 30.3, 26.6 (3C), 19.1, 9.3, 8.7, -4.7, -4.8. IR (neat): 1785 (lactone C=O) cm⁻¹. HRMS (M+H)⁺: calcd: 329.2149; found: 329.2149.
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20. The cooled mixture was diluted with ether and washed sequentially with 10% aqueous NaHCO₃ solution and brine, dried over anhydrous MgSO₄, concentrated, and the residue was purified by column chromatography to yield a mixture of **21** and the corresponding Z alkene isomer (85:15; ratio of the vinyl multiplets in the ¹H NMR spectrum) in 78% yield.
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