is believed to be formed in a manner similar to that reported by Green et al. for the reaction of $[(PhC{\equiv}CPh)_3W(NCMe)]$ with *o*-diphenylphosphanylstyrene.[10] Polydiphenylacetylene is a yellow solid, insoluble in most organic solvents, even boiling dichlorobenzene. It was characterized by solid-state ^{13}C NMR and mass spectrometry. The parent peak at $m/z = 3402$ corresponds to 19 diphenylacetylene units. The ^{13}C NMR spectrum shows signals at $\delta = 125$ and 144 for the aromatic and olefinic carbon atoms, respectively. Possible applications of this polydiphenylacetylene are currently being investigated.

Experimental Section

3: A solution of **1** [7] (300 mg, 0.4 mmol) and iminophosphorane **2a** (141 mg, 0.44 mmol) in dichloromethane (20 mL) was stirred at 25 °C for 16 h. The solvents were removed and the residue was chromatographed on silica gel (15 g) with dichloromethane/hexane (2/5, v/v) as eluent. The eluate was collected and concentrated to give **3** as a white solid. M.p. 178–180 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.48-7.13$ (m, 30H, ArH), 6.50 (s, 2H, NH), 3.47(s, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 220.2$ (W=C), 198.9 (Ph*C*), 181.7 (Ph*C*), 143.9–125.5 (Ph), 45.8 (CH_2). Analysis: calcd for $C_{45}H_{36}N_2W$: C 68.53, H 4.60, N 3.55; found C 68.38, H 4.62, N 3.39.

Colorless single crystals of **3** were obtained by recrystallization from dichloromethane/hexane. Crystal data for **3**: $C_{45}H_{36}N_2W$, $M_r = 788.63$, orthorhombic, space group *Pbca*, $a = 20.589(5)$, $b = 20.463(6)$, $c = 16.503(6)$ Å, $V = 6953(4)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.507$ g cm^{-3}, $\lambda = 0.7107$ Å, $\mu = 34.246$ cm^{-1}, $F(000) = 3144$, $T = 298$ K, crystal dimensions $0.30 \times 0.35 \times 0.70$ mm. All measurements were performed on a Nonius CAD-4 diffractometer and refined by a least-squares treatment. $R_F = 0.039$, $R_w = 0.040$ for 3344 reflections with $I_0 > 2.0\sigma(I_0)$ and 434 variables. The NRCVAX program was used for the computation.[11] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100570. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code + (1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

4: White solid, m.p. 182–183 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.48-7.16$ (m, 30H), 3.81 (t, $^3J(H,H) = 9.3$ Hz, 2H), 3.26 (t, $^3J(H,H) = 9.3$ Hz, 2H), 2.27 (q, $^3J(H,H) = 7.4$ Hz, 2H), 0.03 (t, $^3J(H,H) = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 219.9$, 198.5, 181.6, 143.8–125.5 (Ph*C*), 47.4, 45.4, 43.2, 11.9; analysis: calcd for $C_{47}H_{40}N_2W$: C 69.12, H 4.94, N 3.43; found C 69.10, H 4.91, N 3.38.

5: White solid, m.p. 163–164 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.53-6.35$ (m, 35H), 4.07 (t, $^3J(H,H) = 5.3$ Hz, 2H), 3.43 (t, $^3J(H,H) = 5.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.7$, 177.9, 145.8, 142.2–112.8 (PhC), 44.2, 42.4; analysis: calcd for $C_{51}H_{40}N_2W$: C 70.84, H 4.66, N 3.24; found C 70.77, H 4.73, N 3.33.

Polydiphenylacetylene: Diphenylacetylene (225 mg) and **3** (100 mg, 0.126 mmol) in chlorobenzene were heated to reflux for 48 h. A yellow precipatate (149 mg, 66%) was collected by centrifugation with recovery of starting material (108 mg). ^{13}C NMR (solid state, 75 MHz): $\delta = 144$, 125; IR (KBr) $\tilde{\nu} = 1598$, 1578, 1492, 1441 cm^{-1}; MS (DCI): m/z 3402 ($[M+NH_4]^+$), 3224 ($[M+NH_4-178]^+$), 3046 ($[M+NH_4-2\times178]^+$), etc.

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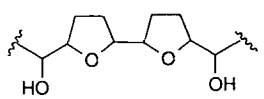
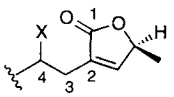
A Convergent Synthesis of (+)-Parviflorin, (+)-Squamocin K, and (+)-5*S*-Hydroxyparviflorin**

Barry M. Trost,* Trevor L. Calkins, and Christian G. Bochet

The diverse bioactivities of the annonaceous acetogenins as antitumor, immunosuppressive, pesticidal, antiprotozoal, anthelmintic, and antimicrobial agents have resulted in considerable attention being focused upon them.[1,2] The acetogenins almost invariably have the butenolide fragment **A** as a head group. Frequently, the most biologically active ones possess a hydroxyl group at C-4 of **A** and a dihydroxy bis(tetrahydrofuran) unit **B** somewhere in the chain.



B



A

Special interest accrues to those members that show remarkable differential cell cytotoxicity. For example, parviflorin (squamocin E, **1**)[3] shows ED_{50} values against human lung, breast, and colon carcinoma of 1.3×10^{-15}, 1.7, and 0.5 respectively. In trying to devise a convenient convergent general strategy to these bioactive acetogenins, we chose parviflorin as a target because of its partially hidden symmetry revealed by our retrosynthetic analysis outlined in Scheme 1. Regio- and diastereoselective introduction of the C-4 hydroxyl

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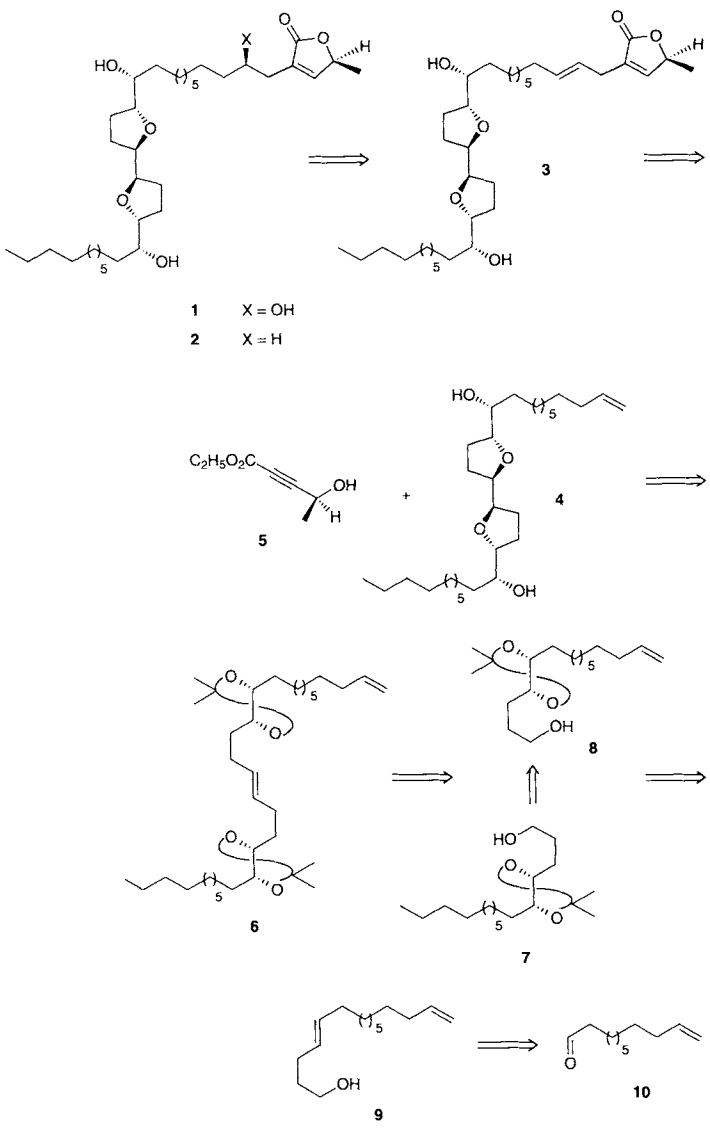


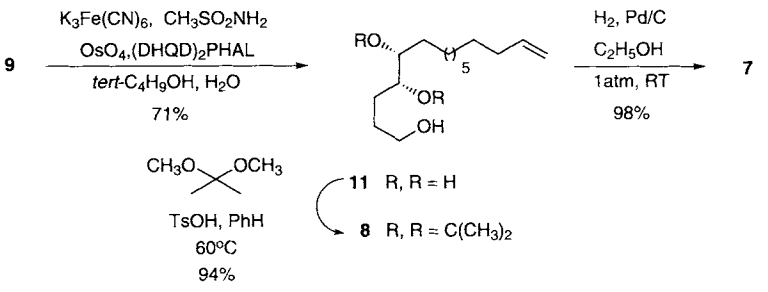
Scheme 1. Retrosynthesis of parviflorin (**1**).

group from an alkene precursor suggests that **3** may be a viable option. Such a precursor is particularly useful, since the double bond can serve as a focal point to diverge to other acetogenins such as squamocin K (**2**) or analogues by chemoselective oxidation at or adjacent to this alkene. The availability of our recently developed Ru-catalyzed Alder–ene type reaction[4] suggests as precursors the alkene **4** and alkyne **5**, which is already readily available from *S*-lactic ester.[4] The bis(tetrahydrofuran) **4** nearly possesses a C_2 symmetry axis; the presence of the terminal double bond is the only feature destroying this symmetry element. Envisioning the *trans*-alkene **6** as the precursor to **4** suggests an olefination to join **7** and **8** to create **6**. It is now obvious that since hydrogenation of **8** creates **7**, the former then becomes both halves of **4** and should readily derive from commercially available 10-undecenal (**10**) via the known **9**.[5] Thus, two units of **8** and one unit of **5** converge to create parviflorin and squamocin K.[6,7] In this paper, we report the realization of Scheme 1.

The first two nearly identical blocks **7**[8] and **8**[8] were synthesized as shown in Scheme 2 from **9**, which was prepared in three steps from **10** as previously described.[5] Dihydroxylation by the Sharpless protocol[9] required monitoring to avoid overoxidation. Stopping the reaction at approximately 2/3 conversion gave diol **11**[8] in 71% yield and 94% *ee*.[10] Protection of the diol gave the first half (**8**)[8] and subsequent catalytic hydrogenation produced the second half (**7**).[8]

The desire for the (*E*)-alkene **6** led us to choose the Julia olefination[11] for the coupling (Scheme 3). To this end, the alkene half **8** was converted straightforwardly into the sulfone **12**[8,12,13] and the alkane **7** into the aldehyde **13**.[8,14] The aldehyde **13** was added to a solution of the lithiated sulfone in THF, and the cold reaction quenched with benzoyl chloride to give adduct **14**[8] reproducibly in 74% yield. Control of the metalation time (30 min) and direct acylation were required to obtain these results. The benzoate **14** was particulary prone to undergo base-catalyzed eliminations under the reductive cleavage conditions even in the presence of numerous buffers. The best in minimizing the simple elimination proved to be boric acid. The alkene **6** was isolated in a 61% overall yield from **12** and **13** as a 3:1 *E*/*Z* mixture. It proved unnecessary to separate the *E*/*Z* mixture, since only the *E* isomer undergoes subsequent dihydroxylation.

The alkene **6** becomes a pivotal intermediate to approach a variety of diastereomeric acetogenins by both the choice of dihydroxylation protocol and hydroxyl group differentiation (in terms of which oxygen becomes the nucleophile and which oxygen the electrophile for formation of the tetrahydrofuran). For the synthesis of parviflorin, **6** was subjected to the Sharpless protocol using $(DHQ)_2PHAL$ to give diol **15**[8] (DHQ–H = dihydroquinine, PHAL = 1,3-phthalazinediyl; Scheme 4) as a single diastereomer, which formed the corresponding mesylate **16**[8] virtually quantitatively. Because hydrolysis of the acetonides was accompanied by partial cyclization, the crude hydrolysate was directly treated with base to give the bis(tetrahydrofuran) **4**. The stage is now set for the butenolide annulation: heating a 1:1 to 1:1.6 ratio of **4**:**5** in methanol at 60°C in the presence of 5 mol% [CpRu(COD)Cl][4] gave 71–98% yields of the butenolide **3**.[8] It is important to note that no protecting groups are required in this reaction. The synthesis of (+)-squamocin K (**2**) only required hydrogenation of the double bond, which proceeded quantitatively with Wilkinson's catalyst[15]



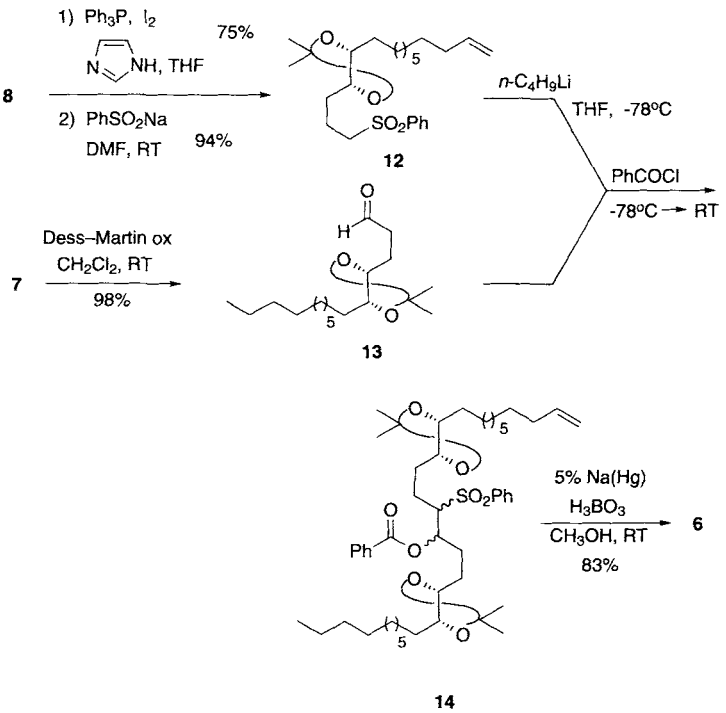
Scheme 2. Synthesis of the building blocks **7** and **8**. Ts = *p*-$CH_3C_6H_4SO_2$.

(C_2H_5OH/PhH (1/1.2), room temperature, 1 atm H_2). Comparison of the infrared and ^1H and ^{13}C NMR spectra of the synthetic and the natural product as well as rotation identified the product.

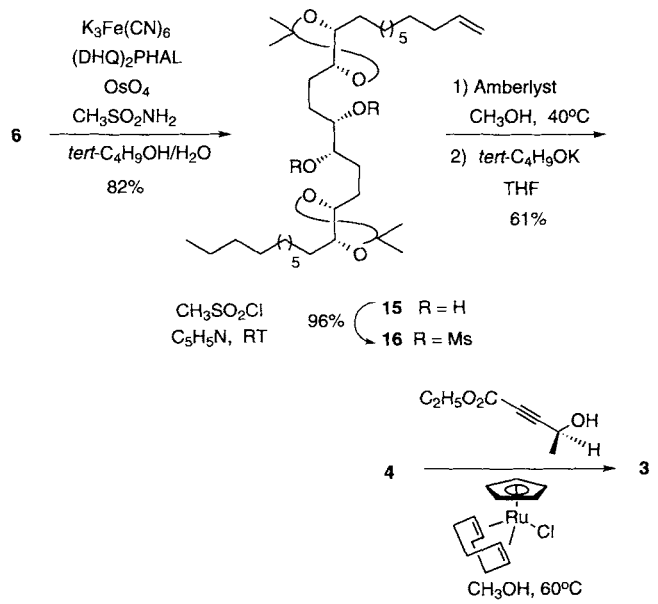
For parviflorin, we must install the C-5 hydroxyl group. The protocol began with a diastereoselective dihydroxylation to (5*S*)-hydroxyparviflorin (**17**,[8] Scheme 5).[16] Chemoselective deoxygenation of the C-5 hydroxyl group takes advantage of

the regioselective opening of an intermediate acetoxonium ion upon treatment with acetyl bromide to give bromoacetate **18**, which simultaneously acetylates the additional two hydroxyl groups. Radical debromination gave parviflorin triacetate **19**, which was readily hydrolyzed under acid conditions to give parviflorin, identical spectroscopically to the natural product.

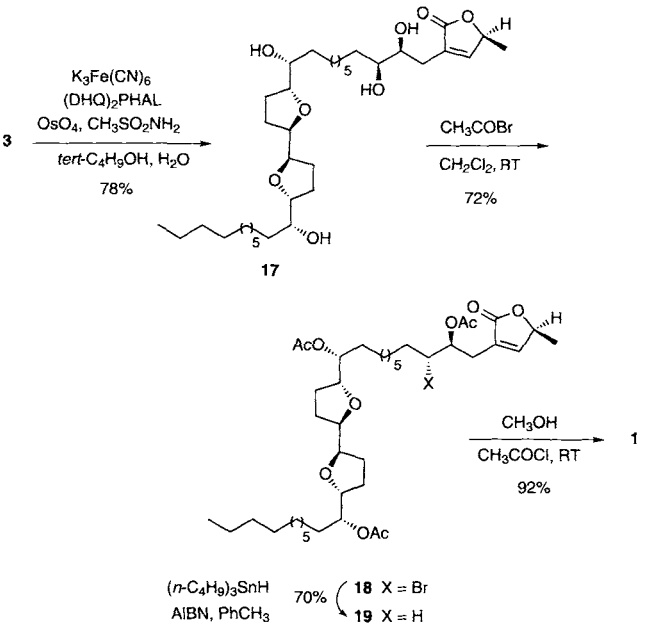
This convergent sequence offers a flexible approach to the bis(tetrahydrofuran) acetogenins. For example, various diastereomers are easily accessed by the method of elaborating the alkene **6**. In addition to the *threo-trans-threo-trans-threo* series, the *threo-cis-threo-cis-threo*, *erythro-trans-threo-trans-*



Scheme 3. Synthesis of alkene **6**.



Scheme 4. Synthesis of butenolide **3**. Ms = CH_3SO_2.



Scheme 5. Synthesis of parviflorin (**1**) from **3**. AIBN = α,α'-azobisisobutyronitrile.

erythro, *erythro-cis-threo-cis-erythro*, *threo-trans-erythro-trans-erythro*, and *erythro-trans-erythro-trans-threo* isomers should be available by manipulation of the oxygen pattern. To demonstrate this principle, *cis*-dihydroxylation of **6** with AD-mix β followed by the same protocol led to the *threo-cis-threo-cis-threo* isomer of **3**. The particular case of parviflorin illustrates the effectiveness of the strategy, since thirty of the carbon atoms and four stereogenic centers derive from a common building block, while the remaining five carbons and an additional stereogenic center are installed by the Ru-catalyzed Alder–ene reaction. Thus, this route should be a versatile approach to the bis(tetrahydrofuran) acetogenins.

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Catalytic Asymmetric Alkylation of Nucleophiles: Asymmetric Synthesis of α-Alkylated Amino Acids**

Barry M. Trost* and Xavier Ariza

Modified peptides not only open a major avenue to understanding biological phenomena, but also offer opportunities for drug discovery.[1] Incorporating conformational constraints probes the molecular structure of receptors. By preorganizing the optimum conformation for binding, significant enhancements of biological activity can be expected. Introduction of alkyl groups at the α-carbon of amino acids introduces such conformational constraints and, furthermore, enhances metabolic stability. As a result, the synthesis of α-alkylated amino acids has attracted considerable attention.[2–6] Virtually all methods involve controlling diastereoselectivity—either by use of a chiral auxiliary[3] or by involving what is termed self-reproduction of chirality (also termed self-regeneration of stereocenters).[4] Methods in which the asymmetric inducing unit is required only catalytically are lacking. The major method for catalytic asymmetric synthesis of simple amino acids,[7a] hydrogenation of dehydroamino acids, is not applicable. We report a new strategy for the synthesis of α-alkylated amino acids, which are important building blocks for peptide synthesis.

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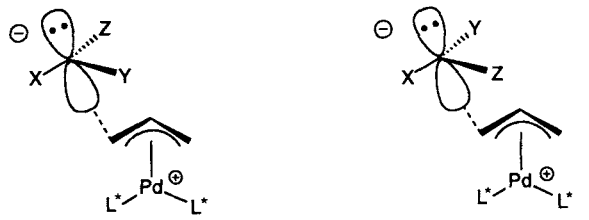
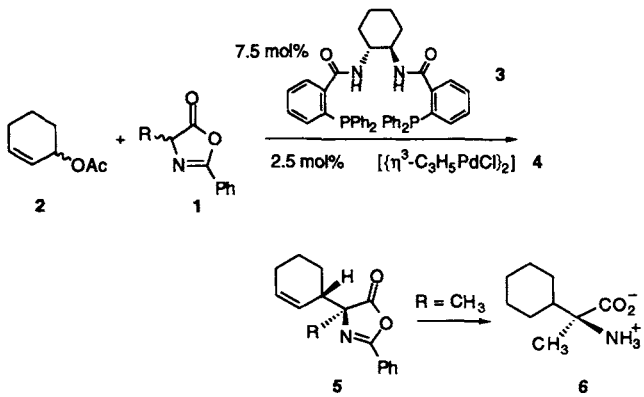
The question relates to the broader one of inducing absolute stereochemistry at an enolate carbon. No reaction is as ubiquitous as alkylations of enolates and related intermediates. The major current approach to effect such reactions asymmetrically involves use of stoichiometric amounts of chiral auxiliaries.[3] Catalytic processes, outside of aldol-like reactions, are rare.[7b,8] An approach based upon palladium-catalyzed allylic alkylations faces the difficult obstacle, illustrated in Scheme 1, that the attacking nucleophile is very remote from the chiral inducing units L*—in fact, the nucleophile is insulated from these chiral ligands by the allyl moiety. It is not surprising that examination of such



Scheme 1. Two competing arrangements for the approach in the asymmetric allylic alkylation at a nucleophilic carbon atom.

reactions to date have been disappointing.[9] Modest success stems from ligands with functional arms that appear to reach beyond the allyl barrier to help direct an incoming nucleophile. We have been exploring a different concept borrowed from the basic principles of an active site of an enzyme.[10] In this model, primary chirality in terms of structural units that contain stereogenic centers induces conformational chirality, which, in turn, creates chiral space. The ability of the reactants to "fit" into the "active site" then defines the molecular recognition and, consequently, the asymmetric induction.

One way to apply this concept to the asymmetric synthesis of α-alkylated amino acids invokes the allylation of the readily available azlactones.[11] The initial studies examined the reaction of the alanine-derived azlactone **1** (R = CH_3) and 3-acetoxycyclohexene (**2**) by using ligand **3** and a palladium complex **4** as a precatalyst (Scheme 2). On use of cesium



Scheme 2. Asymmetric alkylation of azlactones **1** with 3-acetoxycyclohexene **2**.

carbonate as base in dichloromethane at room temperature, a 2.5:1 diastereomeric ratio (d.r.) of alkylation product was obtained in 96% yield. Gratifyingly, the enantiomeric ex-

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