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A novel synthesis of 5-hydroxy-2,2-dimethyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one

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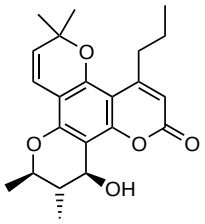
Abstract—A concise synthesis of 5-hydroxy-2,2-dimethyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one utilising a novel selective desulfonylation protocol is described. This method provides facile access to a key intermediate for the asymmetric synthesis of calanolide A.

A family of xanthone natural products with potent antiviral activity has been isolated from plants of the genus *Calophyllum*. In particular, (+)-calanolide A **1**, isolated from *Calophyllum lanigerum* var *austrocoriaceum* is a potent inhibitor of HIV-1 reverse transcriptase.[1]



(+)-Calanolide A **1**

A number of syntheses of calanolide A have been reported,[2] with the syntheses of Deshpande,[2b] Trost[2g] and Ishikawa[2h] being asymmetric. We were interested in the potential of the Trost palladium(0) catalysed asymmetric allylation route[2g] (Scheme 1) as the basis for a commercial manufacturing route of (+)-calanolide A **1**. In this approach the secondary ether **5** is produced in high enantiomeric excess and regioselectivity by allylic alkylation of the phenol **2** with tiglyl methyl carbonate in the presence of the ligand **4** and $Pd_2dba_3{\cdot}CHCl_3$ (Scheme 1). One drawback of this synthesis is that a saturated chromane is used as the phenolic nucleophile and an additional oxidation step is required to produce the desired chromene ring system.

Our approach to calanolide A was to use the unsaturated analogue of **2**, chromene phenol **10** (Scheme 2) as the nucleophile in the asymmetric allylation reaction. Hence, we required an efficient synthesis of the phenol **10**. Only one synthesis of **10** is reported in the literature, in which, 4-*n*-propyl-5,7-dihydroxycoumarin **6** is treated with an excess of 2-methylbut-3-en-2-ol and $BF_3{\cdot}OEt_2$ in 1,4-dioxane, to provide **10** in 3% yield along with a variety of other products.[3] It was apparent that protection of the 7-hydroxyl group was necessary in order to control this annulation process. Initially we tried silyl protection. Thus, reaction of diphenol **6** with triisopropylsilyl chloride and imidazole gave the 7-TIPS compound in 20% yield, along with the 5-TIPS (3%) and the bis-silylated product (10%). However, the TIPS group was found to be unstable to the chromene annulation conditions. Therefore, we were attracted to robust sulfonate esters[4] in preference to more labile protecting groups such as silyl ethers or carboxylate esters.[5]

The 7-monotosylation of 4-methyl-7,8-dihydroxycoumarin has been reported, but in low yield (36%).[6] We were unable to achieve selective 7-monotosylation of the homologous diphenol **6**, the ditosylate **7a** (Scheme 2) being the major product. During our studies in this area we also tried to alkylate the diphenol **6** with tiglyl methyl carbonate **3** under the Trost conditions, with the view that the 7-hydroxyl was less hindered and would hence react selectively with the palladium π-allyl electrophile. This was indeed the case, but a major by-product was the bis-allylated material.[7] It appears that blocking of the 7-hydroxyl group of diphenol **6** leads to an increase in the nucleophilicity of the 5-hydroxyl, making monoprotection problematic.

Keywords: selective desulfonation; chromene synthesis; calanolide A.

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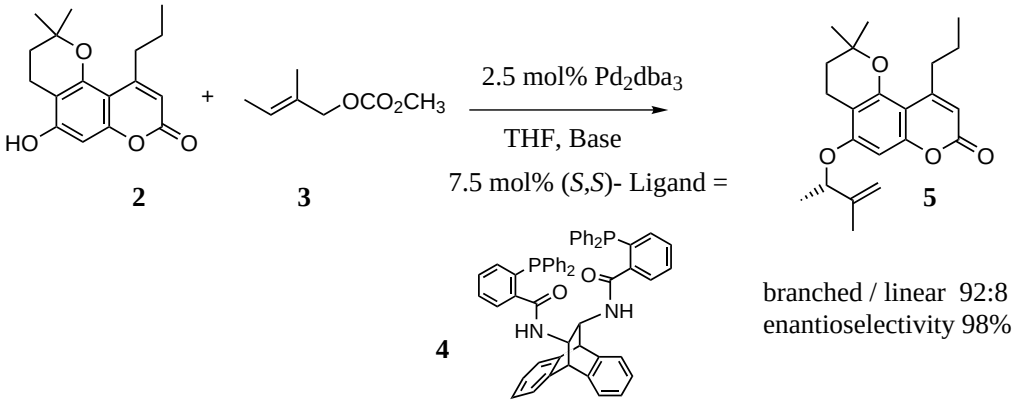
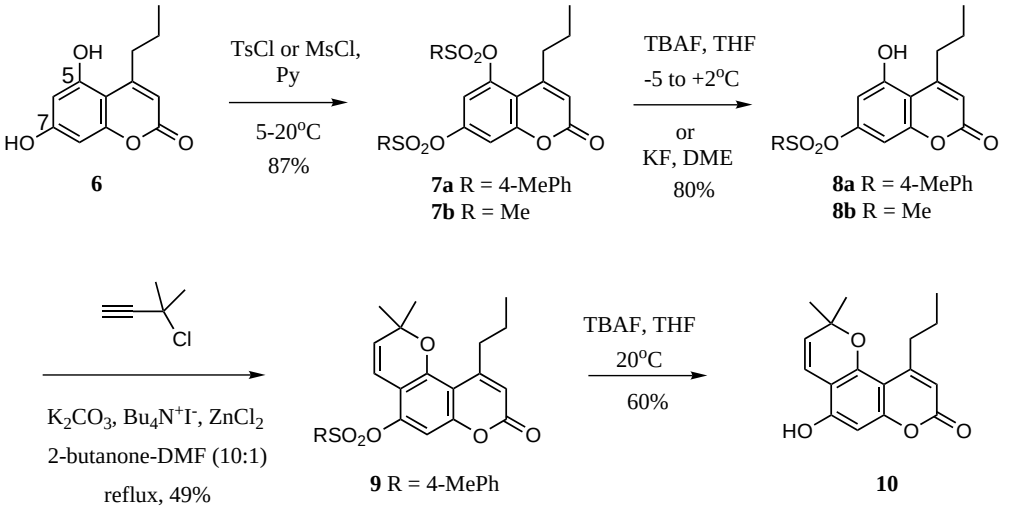


Scheme 1. Palladium(0) catalysed allylation of a key intermediate towards (−)-calanolide A ent-1.

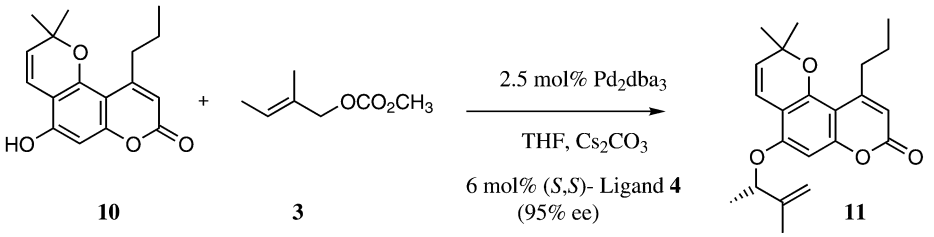


Scheme 2. Selective desulfonation and chromene annulation.

These observations led us to consider selective deprotection, rather than selective protection as a means of obtaining monoprotected derivatives of the diphenol **6**. After removal of one protecting group from a diprotected diphenol under basic conditions, a phenolate anion is produced from which nucleophilic removal of the second protecting group should be disfavoured.

The ditosylate **7a** was readily prepared by the reaction of **6** with tosyl chloride (Scheme 2). Initial attempts to cleave one of the sulfonyl groups were made with sodium hydroxide. However this preferentially opened the lactone, so we turned our attention to the harder nucleophile fluoride.[8] We were pleased to find that treatment of the ditosylate **7a** with tetra-*n*-butylammonium fluoride (TBAF) in THF at or below room temperature gave selectively the 7-monotosylate **8a** (8:1 ratio of regioisomers).[9,10] The minor 5-tosylate was removable by recrystallisation. The same result was obtained with the dimesylate **7b**. The use of inexpensive potassium fluoride as a fluoride reagent in place of TBAF was investigated with the dimesylate **7b**. This reagent was much less reactive, and addition of stoichiometric activators was necessary to obtain any conversion. With tetra-*n*-butylammonium chloride (TBAC) as the activator in acetonitrile as solvent, the reaction proceeded at room temperature to give the 7-monomesylate **8b** in increased selectivity (19:1). The potassium-complexing ligand tris-[2-(2-methoxyethoxy)-ethyl]-amine (TDA-1) was less activating than TBAC, but in DME/water at reflux, **8b** was obtained in a 5.6:1 ratio of regioisomers. The monophenol **8a** was converted to the chromene **9** by annulation with 3-chloro-3-methyl-1-butyne.[2a] The sulfonyl protecting group was entirely stable under these quite vigorous conditions. The remaining sulfonyl group was removed with TBAF to give the desired chromene phenol **10**. Asymmetric allylic alkylation of the phenol **10** with tiglyl methyl carbonate **3** (Scheme 3) gave the intermediate **11** in the synthesis of calanolide A previously reported by Trost.[2g] The enantioselectivity and regioselectivity were similar to those obtained by Trost with the chromane phenol **2**.[11] At the time of this work, the ligand **4** was available to us in 95% enantiomeric excess, but it is likely that significantly higher enantioselectivity would be achievable if ligand **4** of higher enantiomeric excess was used.

Thus, an improved synthesis of calanolide A was demonstrated. We believe that the novel disulfonate



Scheme 3. Palladium catalysed asymmetric allylation of chromene phenol **10**.

monodeprotection methodology developed for this synthesis may be of more general utility in preparing monoprotected derivatives of diphenols. In particular, sulfonyl protecting groups have the virtues of being inexpensive, robust and cleanly removed in the presence of a variety of functionality such as the lactone and two double bonds of **9**.

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7. Reacting the bisphenol **6** with tiglyl methyl carbonate using the Trost conditions gave a 32% yield of the 7-*O*-tiglyl compound (branched/linear 2:1), a 4% yield of the 5-*O*-tiglyl compound (branched/linear 1:1) and a 30% yield of the 5,7-bis-*O*-tiglyl compounds.
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10. In a typical example the ditosylate **7a** (116.3 g, 220 mmol) is suspended in THF (220 ml). The reaction flask is purged with nitrogen, and the suspension is stirred until most of the ditosylate **7a** has dissolved. The suspension is cooled to 0°C, and tetra-*n*-butylammonium fluoride (1 M in THF, 220 ml) is added over 30 min, keeping the temperature in the range −5 to +2°C. During the addition, the ditosylate dissolves to give a dark solution. The solution is stirred at −5 to +2°C for 15 min then ethyl acetate (440 ml), saturated ammonium chloride solution (330 ml) and water (110 ml) are added. The aqueous layer is removed and the organic phase is washed with 0.75 M $KHSO_4$ (800 ml) and 2 M $KHSO_4$ (4×250 ml). During these acid washes, a precipitate of monotosylate **8a** forms in the organic phase. The organic layer is washed with brine-saturated sodium bicarbonate solution (400+100 ml), diluted with acetone (800 ml), dried ($MgSO_4$) and filtered. The $MgSO_4$ is swirled with THF (300 ml), and the suspension is filtered. The combined filtrates are evaporated to dryness. Isopropyl acetate (550 ml) is added, the suspension is heated to reflux and allowed to stir over 15 h while cooling to room temperature. The suspension is filtered and the solid is washed with isopropyl acetate (150 ml) and dried to give the 7-monotosylate **8a** as a fine white solid (65.6 g, 79.6%); mp 210°C; IR ν_{max} (KBr) 3150 (br), 3092, 2967, 1674, 1610, 1429, 1380, 1344, 1289, 1238, 1193, 1180, 1126, 1093, 1047, 1014, 851, 813, 790, 718, 676, 593, 546 and 531 cm^{-1}; ^1H NMR (400

MHz, acetone-d_6) δ ppm 10.3 (1H, brs), 7.82 (2H, d, $J=8.4$ Hz), 7.53 (2H, $J=8.2$ Hz), 6.62 (1H, d, $J=2.4$ Hz), 6.47 (1H, d, $J=2.4$ Hz), 6.08 (1H, s), 2.97 (2H, t, $J=7.7$ Hz), 2.48 (3H, s), 1.67 (2H, sextet, $J=7.4$ Hz) and 1.00 (3H, t, $J=7.3$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.1, 157.4, 157.3, 155.6, 150.8, 146.1, 131.3, 130.4, 128.2, 112.4, 107.3, 105.0, 101.2, 37.1, 22.3, 21.2 and 13.7; (ES) 375 = (M+H$^+$) (100%). Found: C, 60.76; H, 4.76; S, 8.59. $C_{19}H_{18}O_6S$ requires C, 60.95; H, 4.85; S, 8.56%.

11. The enantioselectivity and regioselectivity of **11** were determined by chiral HPLC: Daicel Chiralcel OD column, UV 254 nm, 0.8 ml/min, 1% IPA, 99% heptane. R_T (R) = 14.9 min, R_T (S) = 16.4 min, R_T (linear) = 30.9 min.