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Application of the Cosford cross-coupling protocol for the stereoselective synthesis of (*R*)-(+)-goniothalamin, (*R*)-(+)-kavain and (*S*)-(+)-7,8-dihydrokavain☆

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Abstract—An efficient and versatile synthetic method has been developed and utilized for the stereoselective synthesis of (*R*)-(+)-goniothalamin **1**, (*R*)-(+)-kavain **2** and (*S*)-(+)-7,8-dihydrokavain **3**. Application of the Cosford protocol and direct conversion of aldehydes to β-keto-esters are the key steps in our approach.

Carbon–carbon bond forming reactions represent important processes in organic synthesis. When performed intermolecularly, they are used to couple small fragments to make larger units. Among the numerous methods for carbon–carbon bond formation, palladium-catalyzed transformations have come to play a leading role,[1] and one of the most widely applicable reactions of this type is the arylation of alkynes.

Lactone rings constitute structural features of a broad range of natural products[2] that display important biological activities such as anti-HIV, antifungal, antibacterial, pheromonal, and antitumor properties.[3] α-Pyrones have been utilized as intermediates for synthetic transformations,[4] and much attention has been paid to their synthesis. To the best of our knowledge, this is the first report of the preparation of 6-substituted lactones using arylation of acetylenes.

Goniothalamin, a naturally occurring styryl lactone was isolated in 1967 from the dried bark of *Cryptocarya caloneura*.[5] Later it was isolated from *Cryptocarya moschata*,[6] *Bryonopsis laciniosa*[7] and various species of *Goniothalamus*.[8] Goniothalamin is a potent mosquito larvicide and also shows a weak antibacterial and significant antifungal activity against a wide range of gram-positive and gram-negative bacteria and fungi.[9] It is one of a new class of compounds with potential anticancer properties, displaying cytotoxic, and antitumor properties.[10] (*R*)-Goniothalamin has shown in vitro cytotoxic effects, especially through inducing apoptosis on different cancer cell lines such as cervical carcinoma, gastric carcinoma, breast carcinoma, leukemia, and ovarian carcinoma. In vivo studies have shown that (*R*)-goniothalamin displays tumoricidal and tumoristatic effects on Prague-Dawley rats with 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors.[11] Among the many approaches to goniothalamin,[12] several utilize the Wittig reaction for construction of the styryl double bond. Kavain and dihydrokavain are lactones isolated from the Kava plant (*Piper methysticum*). The kava lactones are believed to be responsible for the biological activity, which include local anaesthetic properties, sedative, analgesic, anticonvulsive, antispasmodic, antimycotic, antifungal, antithrombotic,[13] and central muscular relaxing properties. This has led to its popular use in Europe and North America for the treatment of anxiety disorders. Kava root, commonly available in dietary supplements labeled 'Kava Kava', is also noted for its anxiolytic and soporific qualities. Kavain and dihydrokavain noncompetitively inhibit the specific binding of [3*H*]-β-trachotoxinin-A 20-α-benzoate to receptor site 2 of voltage-gated Na^+ channels.[14] Racemic syntheses of the kava lactones are numerous,[15] but there are fewer enantioselective

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syntheses of (+)-kavain[16] and (+)-dihydrokavain.[17] These two kava lactones differ only in the presence or absence of a double bond linking the two rings.

Delighted by a recent report[18] on a practical and efficient process for the preparation of tazarotene based on a Cosford protocol,[19] and as a part of our program on the synthesis of naturally occurring bio-active lactones,[20] herein, we report the development of a versatile method which involves the Cosford cross-coupling protocol, starting from iodobenzene and an acetylenic alcohol. This novel method utilizes heterogeneous palladium on carbon (Pd/C) as an alternative to the standard homogeneous catalysts for carbon–carbon bond formation. The resulting key intermediate **4** was used for the stereoselective synthesis of goniothalamin, kavain, and 7,8-dihydrokavain[21] (Scheme 1).

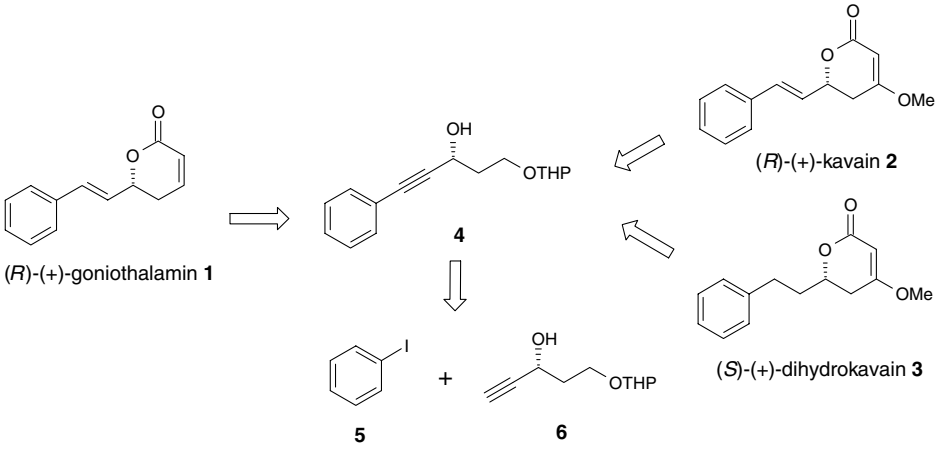
Coupling of iodobenzene **5** and alkyne **6**[22] was achieved by heating in DME/water solution in the presence of K_2CO_3 as base and Pd/C (cat.), CuI (cat.) and PPh_3 (0.1 equiv) to afford the propargylic alcohol **4**[23] in a 90% yield (Scheme 2).

The key intermediate **4** was utilized for the synthesis of **1**, **2**, and **3** as shown in Schemes 3–5. The triple bond in compound **4** was partially reduced using LAH in THF to afford compound **7** in a 90% yield. The secondary hydroxyl group was silylated with TBDMSCl to provide **8** and subsequently the primary THP group was cleaved using PPTS in MeOH to afford compound **9**. The alcohol was subjected to oxidation in the presence of IBX in DCM to furnish the corresponding aldehyde in a good yield, which was subjected to Still's modified Horner–Wadsworth–Emmons reaction to yield the *Z*-olefinic ester **11** in an 80% yield. The TBDMS group was removed using TBAF in THF to afford the hydroxy ester, which on refluxing in benzene in the presence of a catalytic amount of PTSA afforded the target molecule, goniothalamin **1**[24] in a 75% yield (Scheme 3).

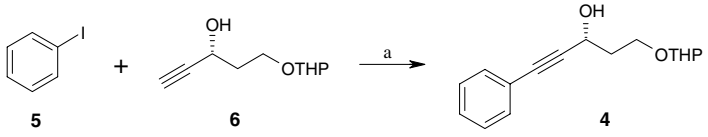
The synthesis of (+)-kavain **2** started from aldehyde **10**, which was converted into β-keto ester **13** by reaction with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride.[25] The TBDMS group was removed using TBAF to afford δ-hydroxy-β-ketoester **14** in an 85% yield. Lactonization of **14** was smoothly accomplished to furnish the target molecule **2**[26] following a reported procedure (Scheme 4).[15a]

The synthesis of 7,8-dihydrokavain **3** started from the key intermediate **4**. The triple bond of compound **4** was reduced using Pd/C in EtOAc to afford fully saturated alcohol **15** in a 90% yield. The secondary hydroxy group was protected and the THP group was cleaved using PPTS in MeOH (Scheme 5). The primary alcohol was oxidized to the corresponding aldehyde **18** in a 90% yield which was then converted into the target molecule **3**[27] in analogous three steps as shown in Scheme 4.

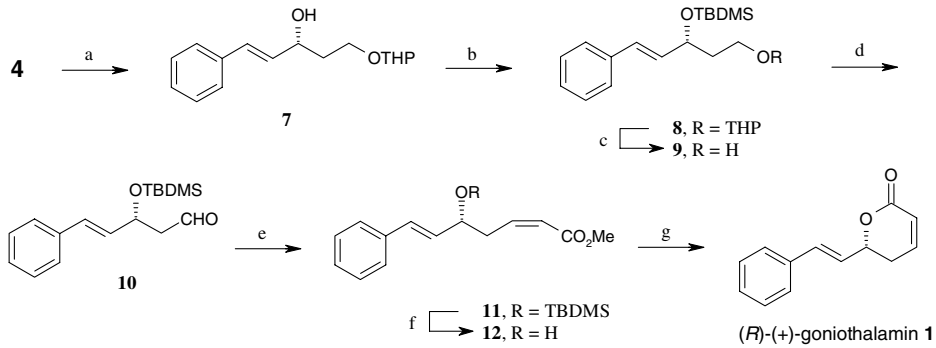
In summary, we have applied a Cosford cross-coupling protocol for the reaction of iodobenzene with an acetylenic alcohol and utilized the intermediate for the synthesis of goniothalamin, kavain, and 7,8-dihydrokavain. This method could readily be extended to a diverse range of coupling partners and, as such, should allow for the rapid generation of novel compound libraries for biological evaluation. This strategy should provide rapid access to the entire family of



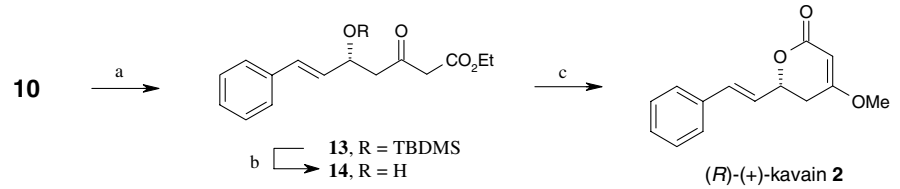
Scheme 1. Retrosynthesis of goniothalamin, kavain, and dihydrokavain.



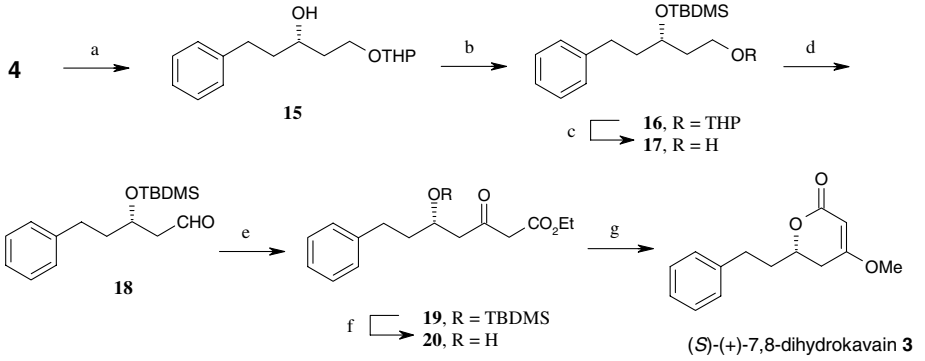
Scheme 2. Reagents and conditions: (a) 10% Pd/C (cat.), CuI (4 cat.), Ph_3P (0.1 equiv), K_2CO_3, H_2O/DME, 80 °C, 2 h, 90%.



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 2 h, 90%; (b) TBDMSCl, imidazole, DCM, DMAP, 2 h, 95%; (c) PPTS, MeOH, 12 h, 90 %; (d) IBX, DMSO, DCM, 0 °C to rt, 2 h, 75%; (e) i. NaH/THF, −78 °C, 30 min; ii. $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, THF, −70 °C, 30 min, 80%; (f) TBAF, THF, 2 h, 80%; (g) benzene, reflux, PTSA, 1 h, 75%.



Scheme 4. Reagents and conditions: (a) anhyd $SnCl_2$ (cat.), $N_2CHCOOEt$, DCM, 0 °C to rt, 40 min, 80%; (b) TBAF, THF, 2 h, 85%; (c) i. K_2CO_3, MeOH, 2 h, ii. $(CH_3)_2SO_4$, acetone, 12 h, 75%.



Scheme 5. Reagents and conditions: (a) Pd/C, EtOAc, 90%; (b) TBDMSCl, imidazole, DCM, DMAP, 2 h, 95%; (c) PPTS, MeOH, 12 h, 90%; (d) IBX, DMSO, DCM, 2 h, 90%; (e) anhyd $SnCl_2$, $N_2CHCOOEt$, DCM, 0 °C to rt, 40 min, 80%; (f) TBAF, THF, 2 h, 85%; (g) i. K_2CO_3, MeOH, 2 h, ii. $(CH_3)_2SO_4$, acetone, 12 h, 75%.

kavalactones and structural analogues. This work is in progress and the results will be published in due course.

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23. *(3R)-1-Phenyl-5-(tetrahydro-2H-2-pyranyloxy)-1-pentyl-3-ol* **4**: pale yellow liquid, $[\alpha]_D^{25}$ −12.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.46–1.88 (m, 6H), 1.93–2.22 (m, 2H), 2.85 (br s, 1H), 3.42–4.24 (m, 4H), 4.59–4.82 (m, 1H), 4.79 (dd, $J = 4.6$, 7.0 Hz, 1H) 7.23–7.31 (m, 3H) 7.35–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 128.1, 122.5, 98.8, 89.4, 84.7, 64.6, 62.1, 61.4, 36.8, 30.3, 25.1, 19.2; IR (neat): 2943, 1618, 1490, 1353, 1200, 1073, 1034, 757, 692 cm^{-1}; LCMS: 283 (M+Na).
24. *R-(+)-Goniothalamin* **1**: white crystalline solid, mp 80–82 °C, lit.[12c] 85 °C; $[\alpha]_D^{25}$ +160 (*c* 1.7, $CHCl_3$), lit.[12c] $[\alpha]_D^{25}$ +164 (*c* 1.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.55 (m, 2H), 5.10 (m, 1H), 6.09 (dt, $J = 9.8$, 1.5 Hz, 1H), 6.25 (dd, $J = 16.0$, 6.2 Hz, 1H), 6.74 (d, $J = 15.9$ Hz, 1H), 6.90 (dt, $J = 9.6$, 4.3 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 77.8, 121.0, 124.9, 126.6, 128.4, 133.2, 134.9, 144.9, 164.1; IR (KBr): 3054, 3026, 2925, 1724, 1242, 814, 691 cm^{-1}; LCMS: 223 (M+Na).
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26. *R-(+)-Kavain* **2**: white crystalline solid, mp 112–114 °C, lit.[15b] 105–106 °C; $[\alpha]_D^{25}$ +121.4 (*c* 1, EtOH), lit.[15a] $[\alpha]_D^{20}$ +124.3 (*c* 1, EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (dd, $J = 17.1$, 4.5 Hz, 1H), 2.67 (dd, J= 17.1, 10.5 Hz, 1H), 3.78 (s, 3H), 5.02–5.10 (m, 1H), 5.20 (s, 1H), 6.25 (dd, $J = 15.8$, 6.0 Hz, 1H), 6.75 (d, $J = 15.1$ Hz, 1H), 7.25–7.45 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.6, 56.5, 76.2, 91.1, 125.8, 127.2, 128.4, 129.3, 133.8, 136.4, 167.4, 172.4.; IR (KBr): 1703, 1624, 1391, 1250, 1233, 1062, 1024, 973, 742, 690; LCMS: 253 (M+Na).
27. *S-(+)-7,8-Dihydrokavian* **3**: white crystalline solid, mp 56–58 °C, lit.[16] 56–58 °C; $[\alpha]_D^{25}$ +33.4 (*c* 1, MeOH), lit.[15a] $[\alpha]_D^{25}$ +31.1 (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.85–2.00 (m, 1H), 2.05–2.20 (m, 1H), 2.30 (dd, $J = 17.0$, 3.9 Hz, 1H), 2.50 (dd, $J = 17.0$, 11.9 Hz, 1H), 2.72–2.95 (m, 2H), 3.72 (s, 3H), 4.30–4.42 (m, 1H), 5.15 (s, 1H), 7.15–7.32 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 33.0, 36.1, 56.1, 74.4, 90.2, 126.1, 128.5, 128.4, 140.8, 167.2, 172.6; IR (KBr): 3026, 2940, 2852, 1706, 1623, 1494, 1454, 1441, 1394, 1372, 1290, 1222, 1094, 1038, 997, 869, 822, 771, 752, 701 cm^{-1}; LCMS: 255 (M+Na).