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A Suzuki Coupling Approach to Double Bonds Locked Analogues of Strobilurin A

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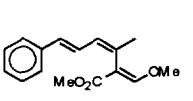
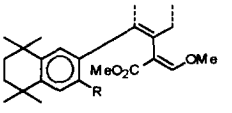
Abstract Four double bonds locked analogues of strobilurin A were first synthesized via palladium(0)-catalyzed cross-coupling reaction of arylboronic acids with vinyl and aryl bromides. Copyright © 1996 Elsevier Science Ltd

The naturally-occurring derivatives of β-methoxyacrylic acid, such as strobilurin A, have become of interest to synthetic chemists and biologists because of their unusual structures and wide range of biological activities.[1] For example, they are able to control the growth of fungi and bacteria, or have insecticidal, antiviral or antitumour activity. However, it was clear that the natural products themselves could not be used directly because of insufficient levels of activity, photochemical instability and volatility.Therefore, research on the synthetic analogues of strobilurin A as fungicides has become of major importance within the agrochemical industry.[2] In order to obtain highly promising fungicides, the synthesis of double bonds locked analogues of strobilurin A (type A) is described hereafter.

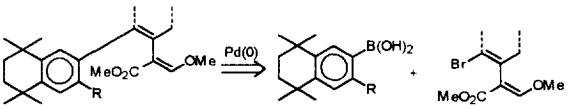


Strobilurin A



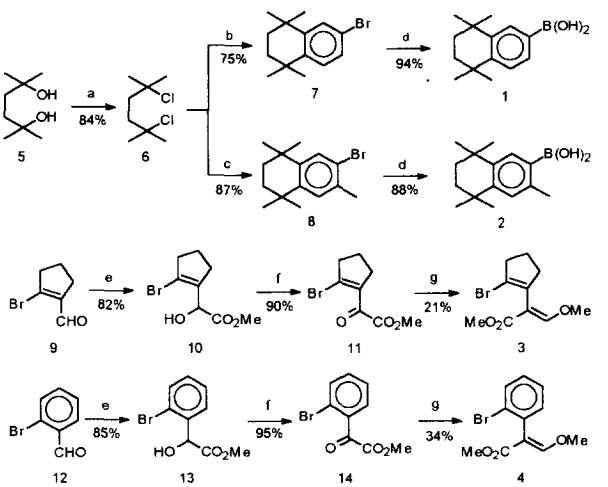
A

Current introductions of the β-methoxyacrylate unit into substrates were carried out at the last steps in the projected synthesis via preparations of an ester or α-keto-ester precursor.[1] Very recently, however, two methods for the direct introduction of this toxophore have been reported. Hodgson's method involved Pd/Cu co-catalyzed reaction of aryl iodides with methyl (Z)-2-tributylstannyl-3-methoxypropenoate.[3] Rossi et al described the cross-coupling reaction between arylzinc chlorides or arylboronic acid and methyl (Z)-2-bromo-3-methoxypropenoate under Pd(0) catalysis. [4] As part of our work in this area we required an efficient synthetic route, which was based on the disconnection shown in Scheme 1 via palladium(0) catalyzed cross-coupling reaction of arylboronic acids with vinyl and aryl bromides in which the methoxyacrylate unit linked directly to a cycloalkene or aromatic ring.



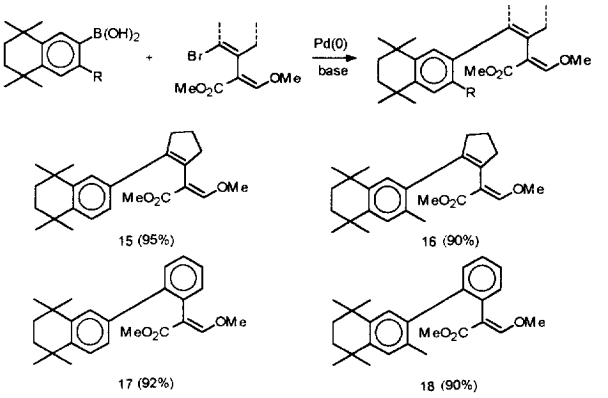
Scheme 1

The Suzuki reaction,[5] palladium catalyzed cross-coupling of boronic acid with an organic electrophile, is one of the best ways of constructing a C-C bond under mild conditions with high functional group tolerance in both coupling partners, and is particularly suited for connecting sp(2)-hybridized centers. The realization of the strategy depicted in Scheme 1 required key precursors arylboronic acid , vinyl and aryl bromides. Arylboronic acids **1** and **2** were easily prepared from the aryl bromides as outlined in Scheme 2. To the best of our knowledge, this new type of bromides has not been appeared. Therefore , a novel and practical preparation of bromides has been developed. Vinyl bromide **3** was synthesized from β-bromoacraldehyde **9** that was prepared from cyclopentanone using the Arnold and Holy's procedure. [6] **9** was very unstable and was treated intermediately with tris(methylthio)methyl-lithium [7] to give , after methanolysis, the α-hydroxyester **10**. Oxidation of **10** with MnO_2 gave the α-ketoester **11**, which was then treated with methoxymethylenetriphenylphosphorane to give the desired vinyl bromide **3**. Similarly, the required aryl bromide **4** was obtained from 2-bromobenzaldehyde **12** which is commercially available. The E-geometry at the acrylate unit was determined by δ_H values of the alkenyl proton (δ_H: 7.56 ppm for the alkenyl proton in aryl bromide **4**): δ_H values for the alkenyl proton in the methoxyacrylates were close to 7.5 ppm which is diagnostic for E-geometry.[8]



Scheme 2 *Reagents and Reaction Conditions* a) concentrated HCl, rt.; b) bromobenzene,$AlCl_3$, CH_2Cl_2, rt.; c) 2-bromotoluene, $AlCl_3$, CH_2Cl_2, rt.; d) *t*-BuLi, -78°C, then $(i\text{-PrO})_3B$, rt., then diluted HCl; e) *n*-BuLi, $CH(SMe)_3$, -78°C, then $HgCl_2$, HgO, aq. MeOH, rt.; f) MnO_2, CH_2Cl_2, rt.; g) Ph_3PCH_2OMeCl, THF, *n*-BuLi, 0°C.

With both arylboronic acids (**1**, **2**) and bromides (**3**, **4**) available, we turned our attention to the application of the Suzuki reaction[5] to the preparation of double bonds locked analogues of strobilurin A. As shown in Scheme 3, the cross-coupling of arylboronic acids and bromides under palladium catalysis afforded the desired analogues **15-18** in excellent yield and proceeded with retention of configuration at the β-methoxyacrylate unit . The structure of these compounds were confirmed by spectral data [9] of IR, ^{1}H-NMR, ^{13}C-NMR and MS.



Scheme 3

The following cross-coupling procedure was representative. Potassium triphosphate trihydrate (5 mmol) was added under N_2 to a solution of arylboronic acid (1.3 mmol), bromide (1 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) in dioxane (10 ml). The mixture was refluxed for 6h and filtrated over silica gel with ethyl acetate. Removal of the solvent in vacuo and flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave a solid in 90-95% yield.

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References and Notes

1. For an excellent review see: Clough, J. M. *Nat. Prod. Rep.* **1993**, *10*, 565.
2. Clough, J. M.; Godfrey, C. R. A. *Chem. in Britain* **1995**, 466.
3. Hodgson, D. M.; Witherington, J.; Moloney, B. A.; Richards, I. C.; Brayer, J.-L. *Synlett.* **1995**, 32.

4. Rossi, R.; Bellina, F.; Carpita, A. *Synlett.* **1996**, 356.

5. a) Suzuki, A. *Acc. Chem. Res.* **1985**, *15*, 178; b) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749; **1986**, *58*, 629; **1991**, *63*, 419; c) Suzuki, A. *Top. Curr. Chem.* **1986**, *130*, 23; d) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221; e) Torrado, A.; Lopez, S.; Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285; f) Hanefeld, W.; Jung, M. *Tetrahedron* **1994**, *50*, 2459.

6. Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059.

7. Dailey, O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216 and references therein.

8. Beautement, K.; Clough, J. M.; De Fraine, P. J.; Godfrey, C. R. A. *Pestic. Sci.* **1991**, *31*, 499.

9. Spectra data of compounds **15-18**:

15 mp.65.5-66°C; ν_{max}/cm^{-1}(KBr): 2962, 1710, 1628, 1495, 1459, 1363, 1127, 911, 830; δ_H(300MHz,$CDCl_3$): 1.23(s, 6H, $2CH_3$), 1.24(s, 6H, $2CH_3$), 1.65(s,4H, $2CH_2$), 1.98(m, 2H, CH_2), 2.68(m, 2H, CH_2), 2.82(m, 2H, CH_2), 3.52(s, 3H, OCH_3), 3.64(s, 3H, OCH_3), 7.05(d, 1H, *J*=8.2Hz, ArH), 7.18(d, 1H, *J*=8.2Hz, ArH), 7.21(s, 1H, olefinicH); δ_C(75MHz,$CDCl_3$): 22.3, 31.9, 34.1, 35.2, 36.7, 37.9, 51.3, 61.5, 109.9, 124.1, 125.0, 125.9, 129.0, 135.7, 140.3, 143.1, 143.9, 158.9, 168.3; *m/z*(EI, 70eV): 368(M^+,27%), 353(9), 336(65), 321(100), 281(41), 267(88), 111(54).

16 mp. 96-96.5°C; ν_{max}/cm^{-1}(KBr): 2958, 1710, 1629, 1498, 1458, 1363, 1250, 1126, 1005, 911, 770; δ_H(300MHz, $CDCl_3$): 1.22(s, 6H, $2CH_3$), 1.24(s, 6H, $2CH_3$), 1.64(s, 4H, $2CH_2$), 2.04(m, 2H, CH_2), 2.16(s, 3H, CH_3), 2.70(m, 4H, $2CH_2$), 3.53(s, 3H, OCH_3), 3.56(s, 3H, OCH_3), 6.95(s, 1H, ArH), 7.01(s, 1H, ArH), 7.03(s, 1H, olefinicH); δ_C(75MHz, $CDCl_3$): 19.4, 23.2, 31.9, 33.9, 35.3, 36.6, 38.3, 51.2, 61.2, 109.1, 126.5, 127.4, 130.6, 132.5, 136.3, 141.3, 142.8, 143.1, 158.7, 168.1; *m/z*(EI, 70eV): 382(M^+, 80%), 367(48), 350(10), 335(100), 291(26), 149(52), 111(31).

17 mp. 87-87.5°C; ν_{max}/cm^{-1}(KBr):2960, 1710, 1635, 1481, 1435, 1363, 1192, 1129, 1003, 911, 830, 769; δ_H(300MHz, $CDCl_3$): 1.24(s, 6H, $2CH_3$), 1.28(s, 6H, $2CH_3$), 1.69(s, 4H, $2CH_2$), 3.46(s, 3H, OCH_3), 3.60(s, 3H, OCH_3), 7.30(s, 1H, olefinicH), 7.00-7.50(m, 7H, ArH); δ_C(75MHz, $CDCl_3$): 31.8, 32.0, 34.1, 34.3, 35.3, 51.3, 61.5, 112.4, 125.8, 126.0, 126.7, 127.1, 127.9, 131.3, 138.9, 142.8, 143.8, 159.2, 168.2, *m/z*(EI, 70eV): 378(M^+,52%), 363(44), 347(54), 331(100), 315(13), 299(35), 215(46).

18 mp. 107.5-108°C; ν_{max}/cm^{-1}(KBr): 2962, 1712, 1626, 1508, 1363, 1238, 1125, 1072, 1000, 834, 767; δ_H(300MHz, $CDCl_3$): 1.20(s, 6H, $2CH_3$), 1.23(s, 6H, $2CH_3$), 1.63(s, 4H, $2CH_2$), 2.09(s, 3H, CH_3), 3.48(s, 3H, OCH_3), 3.59(s, 3H, OCH_3), 6.96(s, 1H, ArH), 7.07(s, 1H, ArH), 7.24(s, 1H, olefinicH), 7.20-7.50(m, 4H, ArH); δ_C(75MHz, $CDCl_3$): 19.6, 32.0, 32.1, 33.6, 33.9, 34.1, 35.2, 35.3, 35.4, 51.3, 61.4, 112.4, 126.6, 127.2, 127.5, 128.3, 129.0, 130.3, 131.3, 132.7, 141.1, 142.4, 143.4, 144.1, 159.2, 168.2; *m/z*(EI, 70eV): 392(M^+, 13%), 377(15), 360(7), 345(45), 301(13), 218(24), 203(100), 161(37).

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