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A Concise Synthesis of a Benzimidazole Analogue of Mycophenolic Acid using a BF_3-Et_2O Catalyzed Amino-Claisen Rearrangement.

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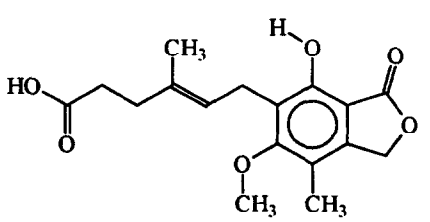
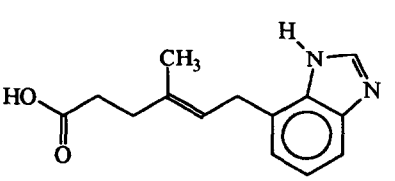
Abstract: *A nine-step synthesis of the benzimidazole analogue, 2, of mycophenolic acid is reported involving both the BF_3-Et_2O catalyzed aromatic amino- and the ortho ester Claisen rearrangements as key steps.*

Keywords: *mycophenolic acid, benzimidazole, aromatic amino-Claisen rearrangement.*

Mycophenolic acid (**1**, "MPA"), produced by the fermentation of a number of penicillium species[1], is a potent inhibitor of *inosine monophosphate dehydrogenase* (IMPD)[2], a rate-limiting enzyme in guanine nucleotide biosynthesis. The compound has been shown to possess significant antineoplastic, antiviral, antiparasitic, and immunosuppressive activity.[3] The attractive features of this drug are low toxicity and the reversal of toxic effects upon withdrawal. The major problem with MPA, however, is that therapeutic blood levels cannot be achieved because of rapid conjugation of the C-7 phenolic hydroxyl group with glucuronic acid.[4] In order to develop potent and metabolically stable inhibitors of IMPD, we designed a series of bicyclic heteroaromatic analogues (*e.g.*, **2**) of MPA in which the metabolically labile phenolic group was replaced by isosteric, "fixed geometry" hydrogen-bond forming N-H groups incorporated into a heterocyclic system. This paper describes a synthetic approach to **2**, a benzimidazole analogue of MPA.



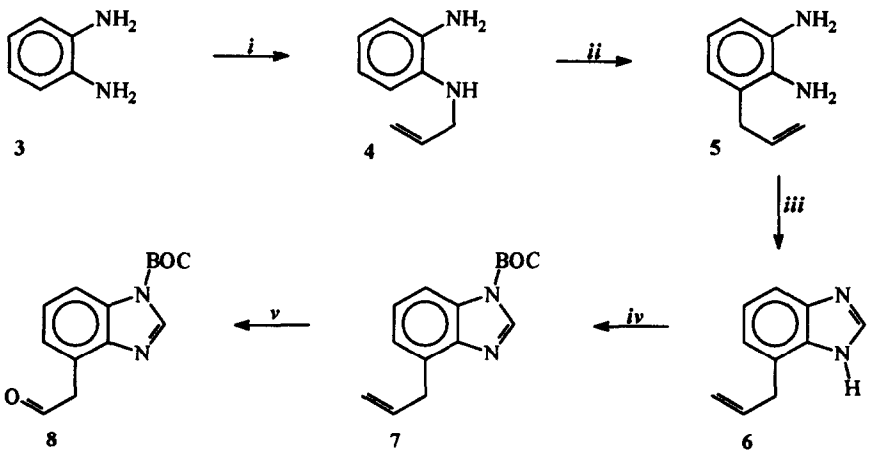
1



2

The synthesis of **2** features both the amino-Claisen rearrangements of the *N*-allylanilines **4** and **10** and the ortho ester Claisen rearrangement of the allylic alcohol **12** into the methyl ester **14**. Thus, 1,2-phenylenediamine (**3**) was treated with allyl bromide (0.5 equiv) in DMF to give *N*-allyl-1,2-phenylenediamine (**4**) in 77% yield (**Scheme 1**). A solution of **4** and BF_3-Et_2O (0.5 equiv) in sulfolane under argon was heated at 190-195 °C to give the rearranged product 3-allyl-1,2-phenylenediamine (**5**) as a yellow solid (mp 40.5-42 °C, 53%).

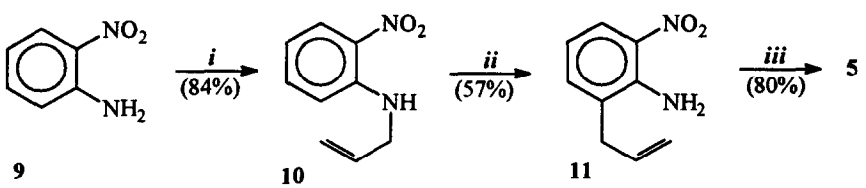
Scheme 1.[a]



[a](*i*) CH_2=$CHCH_2Br$, DMF; (*ii*) BF_3-Et_2O, sulfolane, 190-195 °C; (*iii*) HCO_2H, 80 °C; (*iv*) Boc_2O, dioxane, 80 °C; (*v*) OsO_4-$NaIO_4$, THF-H_2O (3:1)

It has been found in this laboratory[5] that boron trifluoride etherate (BF_3-Et_2O) can efficiently catalyze a variety of aromatic amino-Claisen rearrangements. For example, in anothe three step synthesis of the diamine **5** *N*-allyl-2-nitroaniline (**10**) was subjected to the BF_3-Et_2O catalyzed rearrangement to give 2-allyl-6-nitroaniline (**11**) (**Scheme 2**). Under similar conditions, methyl *N*-allylanthranilate (prepared from methyl anthranilate and allyl bromide in 83 % yield) and 3-(*N*-allylamino)anisole rearranged under BF_3-Et_2O catalysis to give methyl 3-allylanthranilate (52%) and 4-allyl-3-aminoanisole (43%), respectively. The rearrangement of **4**, **10**, methyl *N*-allylanthranilate, and 3-(*N*-allylamino)anisole illustrates the range of aromatic substituents tolerated by the reaction.

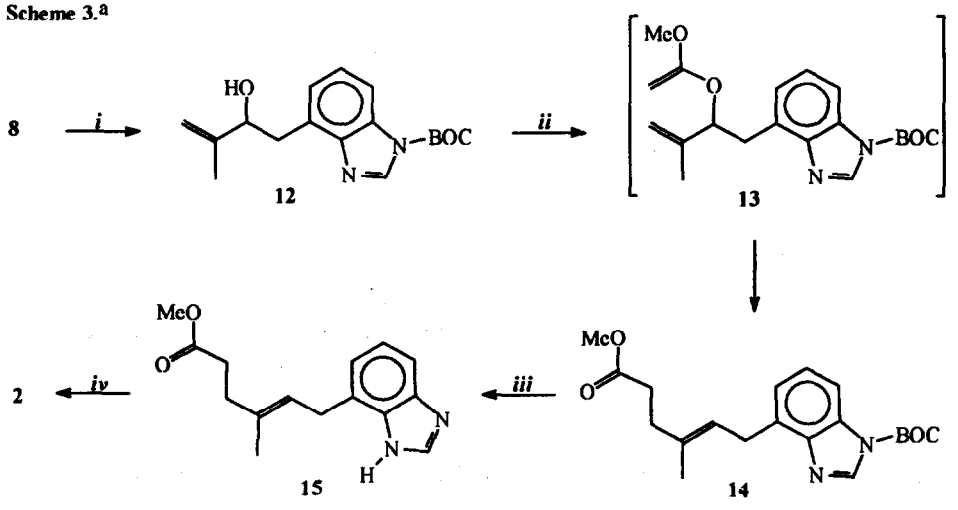
Scheme 2.[a]



[a](*i*) CH_2=$CHCH_2Br$, DMF; (*ii*) BF_3-Et_2O, sulfolane, 160-170 °C; (*iii*) $SnCl_2.2H_2O$, EtOAc, 45 °C.

Treatment of **5** with formic acid[6] afforded 4(7)-allylbenzimidazole (**6**), which, without purification, was directly converted to the *tert*-butoxycarbonyl derivative **7** in 87% overall yield (from **5**). Subsequent oxidation of **7** with OsO_4-$NaIO_4$ in THF-H_2O (3:1) at room temperature provided the requisite aldehyde **8** (mp 84-87 °C, 69%). The aldehyde **8** was treated with isopropenyl magnesium bromide, prepared from isopropenyl bromide and magnesium turnings in THF, to afford the allylic alcohol **12**[7] (**Scheme 3**). This alcohol was used without purification and treated with excess trimethyl orthoacetate (8-13 equiv) and a catalytic amount of propanoic acid (0.2-0.4 equiv) under argon at 105-110 °C for 12 h to give the corresponding ester **14** as a yellow, oily liquid (29% overall yield from **8**).[7-9]

Scheme 3.[a]



[a](*i*) CH_2=$CHCH_2Br$, DMF; (*ii*) $CH_3C(OCH_3)_3$, $CH_3CH_2CO_2H$, 105-110 °C; (*iii*) TFA, CH_2Cl_2; (*iv*) KOH, EtOH, H_2O.

Cleavage of the BOC group in **14** with TFA in CH_2Cl_2 afforded **15** (90%), and alkaline hydrolysis of the ester in **15** furnished the target compound **2** as a white solid (mp 161-163 °C, 85%).[10] Thus, the synthesis of **2** was realized in 5.5% overall yield in nine steps from commercially available 1,2-phenylenediamine.

In conclusion, the short, convenient synthetic approach to **2** may easily be extended to the preparation of a series of 2-substituted benzimidazole analogues of mycophenolic acid with the completely elaborated hexenoic acid side chain. This approach should also prove valuable for the synthesis of other heterocyclic analogues of mycophenolic acid with bioisofunctionally equivalent hydrogen bonding groups replacing the phenol. Further work on the synthesis and biological evaluation of these analogues is in progress.

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References and Notes

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10. All new compounds were characterized by ^{1}H NMR (300 MHz) and IR spectrometry. The spectral data and elemental analyses for the advanced intermediate **14** and the target compound **2** are given below:

Methyl (*E*)-6-[1-(*tert*-Butoxycarbonyl)benzimidazol-4-yl]-4-methyl -4-hexenoate (14): ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.31 (t, J = 7.6 - 8.1 Hz, 1 H), 7.14 (d, J = 7.7 Hz, 1 H), 5.50 (t, 1 H), 3.79 (d, J = 7.5 Hz, 2 H), 3.63 (s, 3 H), 2.47-2.35 (m, 4 H), 1.78 (s, 3 H), 1.70 (s, 9 H); IR (neat) 2987, 1740, 1426, 1369, 1276, 1257, 1150, 1108 cm^{-1}; CIMS m/e 359 (MH^+, 4), 259 (100). HRMS calcd for $C_{20}H_{26}N_2O_4$ (MH^+): 359.19708. Found: 359.19720. Anal. calcd for $C_{20}H_{26}N_2O_4$: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.94; H, 7.33; N, 7.85.

(*E*)-6-[Benzimidazol-4(7)-yl]-4-methyl-4-hexenoic Acid (2): ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 7.59 (d, J = 7.3 Hz, 1 H), 7.22 (t, J = 7.3-8.1 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H), 5.70 (t, 1 H), 3.76 (d, J = 7.3 Hz, 2 H), 2.72 (t, 2 H), 2.51 (t, 2 H), 1.88 (s, 3 H); IR (KBr) 3451, 3125, 2917, 2855, 1567, 1420 cm^{-1}; CIMS *m/e* 245 (MH^+, 100). HRMS calcd for $C_{14}H_{16}N_2O_2$ (MH^+): 245.12900. Found: 245.12840. Anal. calcd for $C_{14}H_{16}N_2O_2$(+0.25 H_2O): C, 67.58; H, 6.69; N, 11.26. Found: C, 67.62; H, 6.63; N, 11.27.

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