Tetrahedron Letters 53 (2012) 4444–4446

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nitromethyl benzoate annulation reactions: a rapid construction of the stealthin skeleton

George A. Kraus *, Divya Chaudhary, Yi Yuan, Andrew Schuster

Department of Chemistry, Iowa State University, Ames, IA 50011, United States

ARTICLE INFO

Article history:
Received 11 May 2012
Revised 8 June 2012
Accepted 11 June 2012
Available online 16 June 2012

Keywords:
Annulation
Quinone
Stealthin
Nitro
Carbanion

ABSTRACT

The annulation of 2-(nitromethyl)benzoates with enones gave 4-nitro-1-naphthols in good yields. The carbocyclic framework of the stealthins was synthesized.

Quinones can be conveniently and regioselectively prepared using annulation reactions with phthalide **1** or ester **2** and suitable Michael acceptors.[1–3] As part of a program to enhance natural antioxidants,[4] we needed a flexible synthesis of the stealthin skeleton shown in Figure 1. Stealthin A (**3**) and stealthin C (**4**) are members of a class of tetracyclic natural products isolated from *Streptomyces viridochromogenes*.[6] Stealthin A inhibited peroxylipid formation at IC_{50} of 0.04 mg/mL versus 10.8 mg/mL for vitamin E.[7] Syntheses of these compounds were reported by Snieckus and others.[8] Although a cyclopentenone or an indenone would be the logical Michael acceptor, annulation reactions involving cyclopentenones and indenones can proceed in low yields due to their sensitivity to strongly basic conditions. Based on reports that nitroalkanes undergo efficient Michael addition to cyclopentenones,[5] we envisaged a direct route to compounds such as **3** or **4** beginning from indenones. Our route generates the naphthol more efficiently than previous approaches.

Ester **5** was readily prepared in 32% yield from the methyl ester of ortho-toluic acid by bromination followed by displacement of the bromide with silver nitrite in ether.[9] As shown in Scheme 1, ester **5** was treated with cyclopentenone in acetonitrile to form the Michael adduct which cyclized using NaOMe in THF in 54% yield. Conversion to phenol **6** proceeded smoothly using DDQ in toluene or air in DMSO.[10]

The successful annulation with cyclopentenone prompted us to examine indenone and other Michael acceptors. The reaction of **5** with indenone, dicyclopentadienone,[11] tetrahydroindenone, and phenyl vinyl ketone afforded phenols **7**, **8**, **9**, and **10** in yields of 64%, 47%, 27%, and 22%, respectively, as shown in Figure 2. The melting point of **10** matched that reported in the literature.[12]

Our strategy for assembling the stealthin skeleton, depicted below in Scheme 2, begins with ester **11**, readily available from ethyl acetoacetate.[13] Benzylic bromination using NBS and AIBN in benzene produced the benzylic bromide in 75% yield. Treatment with silver nitrite in ether produced ester **12** in 50% yield.

Indenone **14** was prepared from 6-methyldihydrocoumarin (**13**) as shown in Scheme 3. An intramolecular Friedel–Crafts acylation generated the indanone in 71% yield. The phenol was protected as a benzenesulfonate in 87% yield. Treatment with HIO_3 in DMSO[14] afforded indenone **14** in 87% yield.

As shown in Scheme 4, the reaction of **12** and **14** with DBU in acetonitrile produced a Michael addition product in 72% yield. The product was treated at −78 °C with 2.2 equiv of lithium diisopropylamide (LDA) to generate tetracyclic ketone **15** in 23% yield.

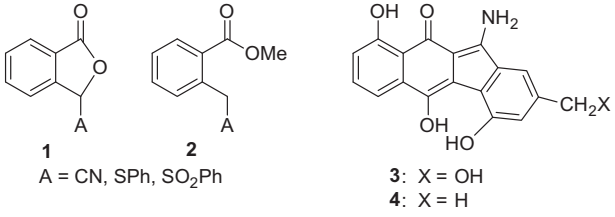

Figure 1. Stealthin skeleton.

* Corresponding author. Tel.: +1 515 294 7794; fax: +1 515 294 0105.
E-mail address: gakraus@iastate.edu (G.A. Kraus).

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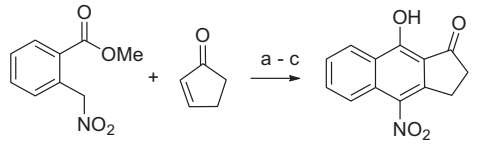
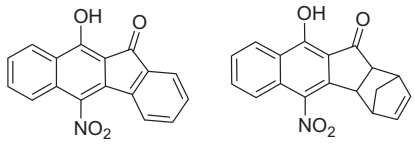
http://dx.doi.org/10.1016/j.tetlet.2012.06.051

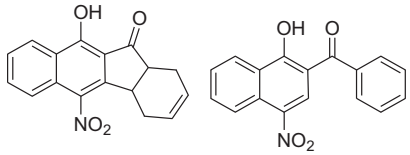


5 6

Scheme 1. Reagents and conditions: (a) Bu_4NOH, MeOH 74%; (b) NaOMe, THF 54%; (c) air, DMSO 90%.

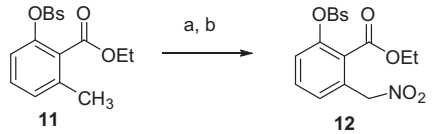


7 8



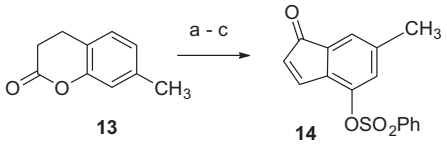
9 10

Figure 2. Adducts of **5** with enones.



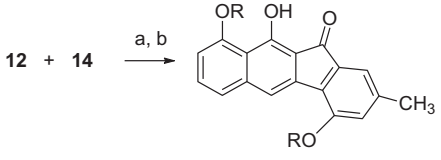
11 12

Scheme 2. Reagents and conditions: (a) NBS, AIBN, benzene reflux, 75%; (b) $AgNO_2$, ether 0 °C–rt, 50%.



13 14

Scheme 3. Reagents and conditions: (a) $AlCl_3$, NaCl, 200 °C, 71%; (b) Et_3N, $PhSO_2Cl$, THF, rt, 87%; (c) HIO_3, DMSO 50 °C, 87%.



15: R = $PhSO_2$
16: R = H

Scheme 4. Reagents and conditions: (a) DBU, CH_2Cl_2, 0 °C, 72%; (b) 2.2 equiv LDA, THF, −78–0 °C, 23%.

In summary, the Michael addition/Claisen condensation sequence affords good overall yields of tricyclic and tetracyclic adducts.[15] It provides an effective route to tetracyclic stealthin analogs. This pathway will permit the synthesis of an array of analogs similar to **15** for biological testing.

Acknowledgments

We thank the Iowa State Department of Chemistry for undergraduate research support for AS and for graduate student stipend support for DC.

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15. *Representative experimental:*
Representative synthesis of compound **7**
To a solution of nitro ester **5** (0.196 g, 1.0 mmol) and 1H-inden-1-one (0.130 g, 1.0 mmol) in acetonitrile (3 mL) was added triton B solution in methanol (0.085 mL, 40% w/w, 0.2 equiv) at 0 °C. The temperature was allowed to reach rt and the reaction was monitored by TLC. Then the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. Purification on column chromatography on silica gel using EtOAc/hexane as eluent gave 0.221 g of the open-chain intermediate in 68% yield. Intermediate: mixture of two diastereoisomers in a ratio of 3:2. Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 8.06 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.77 (m, 1H), 7.71 (m, 2H), 7.56 (m, 2H), 7.39 (m, H), 7.07 (d, *J* = 8.0 Hz, 1H), 4.42 (m, 1H), 3.73 (s, 3H), 2.81 (m, 2H), 2.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz):203.7, 166.7, 151.7, 137.8, 135.6, 134.8, 134.2, 133.4, 131.8, 130.2, 129.8, 127.6, 126.0, 124.2, 88.7, 63.0, 42.6, 40.9. Minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 7.99 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.38 (m, 1H), 6.79 (d, *J* = 10.8 Hz, 1H), 6.66 (m, 1H), 4.63 (m, 1H), 3.82 (s, 3H), 2.80 (m, 2H), 2.41 (m, 1H). ^{13}C NMR (CD_3COCD_3, 100 MHz): 203.2, 167.2, 152.9, 137.1, 135.0, 134.5, 134.0, 133.4, 131.4, 130.4, 129.3, 127.6, 126.1, 124.5, 88.4, 52.8, 42.0, 40.0.
To a solution of intermediate (0.174 g, 0.535 mmol) in THF (20 mL) was added a solution of sodium methoxide in methanol (0.238 mL, 4.5 M, 2 equiv) at 0 °C, and it was stirred at rt. After the disappearance of the starting material on TLC, it was quenched with ice, followed by a saturated NH_4Cl solution. The crude product was extracted with EtOAc, dried over $MgSO_4$, and the solvent was removed under vacuo. Then the crude product was dissolved in toluene (2 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.123 g, 0.554 mmol, 1 equiv) was added in portion at 0 °C. The reaction was stirred at rt. After the reaction was finished ice was added and it was extracted with EtOAc and purification on column chromatography on silica gel gave 0.100 gram of compound **7** in 64% yield. Compound **7**: ^{1}H NMR (CD_3COCD_3, 300 MHz): 8.25 (t, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.70 (m, 2H), 7.62 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H). (EI) *m*/*z* Calculated for $C_{17}H_9NO_4$: 291.0532, Found: 291.0536.
Compound **6**: ^{1}H NMR (CD_3COCD_3, 400 MHz): 8.46 (m, 2H), 7.96 (t, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 3.58 (m, 2H), 2.58 (m, 2H). HRMS (EI) *m*/*z* Calculated for $C_{13}H_9NO_4$: 243.0532; Found: 243.0535.
Compound **8**: ^{1}H NMR ($CDCl_3$/CD_3COCD_3, 400 MHz): 8.40 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 5.98 (m, 1H), 5.61 (m, 1H), 4.44 (m, 1H), 3.43 (m, 2H), 2.68 (m, 1H), 1.80 (m, 2H).
Compound **9**: ^{1}H NMR ($CDCl_3$/CD_3COCD_3, 400 MHz): 8.38 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 5.85 (m, 1H), 5.71 (m, 1H), 4.23 (m, 1H), 3.09 (m, 1H), 2.59 (m, 2H), 2.42 (m, 2H). HRMS (EI) *m*/*z* Calculated for $C_{17}H_{13}NO_4$:295.0845; Found: 295.0848.
*10-hydroxy-2-methyl-11-oxo-11H-benzo[b]fluorene-4, 9-diyl dibenzenesulfonate (**15**).* To a stirred solution of ethyl 2-(nitromethyl)-6-((phenylsulfonyl) oxy)benzoate, **12** (968 mg, 2.65 mmol) and 6-methyl-1-oxo-1H-inden-4-yl benzenesulfonate, **14** (398 mg, 1.33 mmol) in 10 mL acetonitrile was added

DBU (0.4 ml, 2.65 mmol) at 0 °C and stirred at rt overnight, where it was worked up with 5% aqueous HCl and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification via silica gel chromatography (40% ethyl acetate in hexanes) yielded the desired Michael adduct (637 mg, 72% yield).

To a stirred solution of freshly prepared LDA (2.2 equiv) in THF at −78 °C was added a solution of the Michael adduct (405 mg, 0.61 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to rt, where it was stirred for 3 h. The reaction mixture was then worked-up with aqueous NH_4Cl and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification via silica gel chromatography (30% ethyl acetate in hexanes) yielded the desired cyclized product as a yellow compound (86 mg, 25% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 7.2 Hz, 4H), 7.66–7.62 (m, 2H), 7.53–7.51 (m, 6H), 7.46–7.43 (m, 2H), 7.32 (s, 1H), 7.11(d, J = 8.1 Hz, 1H), 7.09 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.62, 113.64, 116.39, 119.76, 121.49, 123.67, 128.61, 128.94, 129.22, 129.60, 130.13, 132.73, 134.47, 134.98, 136.19, 138.52, 141.35, 142.03, 145.56, 147.72, 156.65, 194.28.

HRMS (EI) m/z exact mass calculated for $C_{30}H_{21}O_8S_2$ $[M+H]^+$: 573.0672. Found 573.0677.