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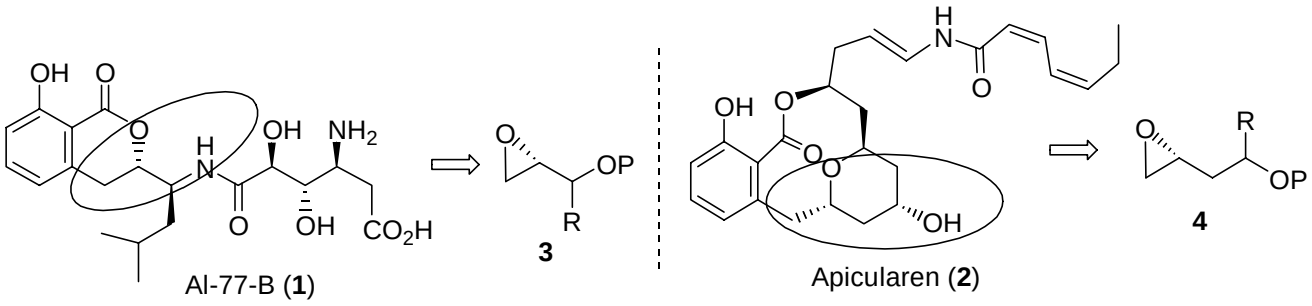
SYNTHESIS OF THE KEY INTERMEDIATES FOR THE CORE 3,4-DIHYDROISOCOUMARIN STRUCTURES OF AI-77-B AND APICULAREN FROM *ORTHO*-METALLATED DIANIONS OF *t*-BUTYLBENZAMIDES AND FUNCTIONALIZED EPOXIDES

Bo-Sung Kwon and Jinsung Tae*

Center for Bioactive Molecular Hybrids (CBMH), Department of Chemistry, Yonsei University, Seoul 120-749, Korea

Abstract – 3,4-Dihydroisocoumarins functionalized with alkoxy substituents were efficiently synthesized from dianions generated by *ortho*-metallation of *t*-butylbenzamides with alkoxy substituted epoxides.

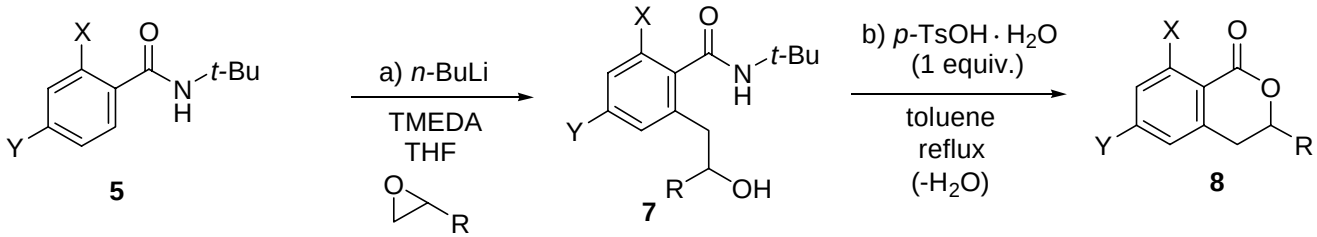
The 3,4-dihydroisocoumarin derivatives are commonly found in many natural products, for example, AI-77-B (**1**) and apicularen (**2**), and exhibit a wide range of important biological properties.[1,2] General approaches for this class of compounds[3] include Diels-Alder / retro-Diels-Alder sequence of acetylenic esters[4] and the reaction of aldehydes with benzylic anions.[5] The epoxide-opening reaction of *ortho*-metallated benzamide derivatives[6] is another method. However, this reaction sequence has not been well studied for the synthesis of complex natural products. Epoxides functionalized with an alkoxy group (such as **3** and **4**) have yet to be investigated in this reaction sequence. The core structures of AI-77-B (**1**) and apicularen (**2**) could be readily accessible by this method using epoxides (**3**) and (**4**) (Scheme 1).



Scheme 1

Herein, we report our preliminary results related to the synthesis of the functionalized 3,4-dihydroisocoumarin derivatives starting from *t*-butylbenzamides and epoxides.

t-Butylamide was used as a directing group, and after coupling, it was removed during lactone formation.[7] Commercially available epoxides (**6a** and **6b**) were first examined. The directed *ortho*-metallation was accomplished with 2.2 equivalents of *n*-butyllithium in the presence of 2.2 equivalents of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) at -78 ^{o}C (Scheme 2).[8,9] Coupling **6a-b** with **5a-c** produced the corresponding alcohol products (**7a-f**) in moderate yields (55-76%). When a catalytic amount of *p*-TsOH • H_2O (*p*-toluenesulfonic acid monohydrate) was used for lactonization, the reaction did not go to completion. In order for this reaction to reach the completion point, 1 equivalent of *p*-TsOH • H_2O was required possibly due to the generation of *t*-butylamine during the reaction. Lactonizations were completed in less than 2 hours and in high yields as shown in Scheme 2. Therefore, the overall yield for both steps ranged from 49 to 74%.



5a: X = H, Y = H
5b: X = OMe, Y = H
5c: X = OMe, Y = Me

6a: R = Me
6b: R = *n*-Pr

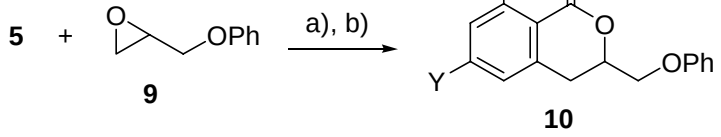
5	6	→ 7	→ 8	overall yield
5a	**6a**	**7a** (69%)	**8a** (96%)	66%
5b		**7b** (76%)	**8b** (97%)	74%
5c		**7c** (74%)	**8c** (95%)	70%
5a	**6b**	**7d** (55%)	**8d** (89%)	49%
5b		**7e** (66%)	**8e** (96%)	63%
5c		**7f** (70%)	**8f** (95%)	67%

Scheme 2

After the general reaction conditions were established, the couplings of alkoxy functionalized epoxides were investigated. When glycidyl phenyl ether (**9**) was reacted with dianions of **5a-c**, the desired products (**10a-c**) were obtained in 48-56% yields (Scheme 3). In general, the amides with *ortho*-methoxy group (**5b** and **5c**) were better substrates than the unsubstituted amide (**5a**). The lactonization yields were uniformly good; the overall two-step yields were 44-50%.

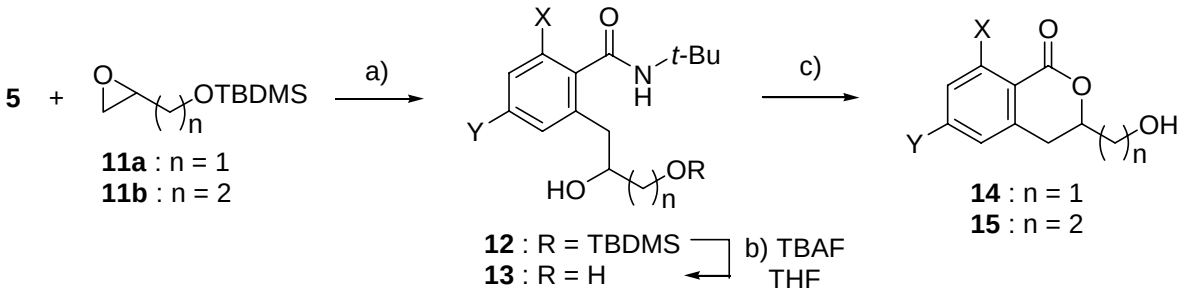
In order to utilize the alkoxy functionality for further manipulations, *O*-protecting groups that can be deprotected under mild conditions were introduced. Unfortunately, the benzyl protected glycidol was unreactive under the same reaction conditions, but the starting epoxide and amides were recovered. Since

the chelating nature of benzyl ether may have interrupted the reactivity of the dianions, a non-chelating silicon protecting group was examined.



5 →	alcohol →	10	overall yield
5a	48%	**10a** (91%)	44%
5b	56%	**10b** (89%)	50%
5c	52%	**10c** (94%)	49%

Scheme 3. Reaction conditions: a) **5**, *n*-BuLi (2.2 equiv.), TMEDA (2.2 equiv.), THF, -78 ^{o}C, 2 h; **9** (1.5 equiv.), -78 to 25 ^{o}C; b) *p*-TsOH • H_2O (1.0 equiv.), toluene, reflux.



5 + 11a	a) → 12	b), c) → 14	overall yield
5a	**12a** (46%)	**14a** (90%)	41%
5b	**12b** (63%)	**14b** (85%)	54%
5c	**12c** (62%)	**14c** (88%)	55%

5 + 11b	a) → 12	b), c) → 15	overall yield
5a	**12d** (51%)	**15a** (92%)	47%
5b	**12e** (68%)	**15b** (88%)	60%
5c	**12f** (66%)	**15c** (91%)	60%

Scheme 4. Reaction conditions: a) **5**, *n*-BuLi (2.2 equiv.), TMEDA (2.2 equiv.), THF, -78 ^{o}C, 2 h; **11** (1.2 equiv.), -78 to 25 ^{o}C, 8 h; b) TBAF, THF, 25 ^{o}C; c) *p*-TsOH • H_2O (1.0 equiv.), toluene, reflux.

Coupling of the TBDMS-protected glycidol (**11a**) with dianions **5a-c** furnished **12a-c** (Scheme 4) in 46-63% isolated yields. Deprotection of TBDMS group of the intermediates (**12a-c**) with TBAF followed by lactonization produced the alcohol products (**14a-c**).[10] Similarly, the analogous epoxide (**11b**) was transformed into **15a-c** in three steps. The three-step overall yields were 47-60%. To the best of our knowledge, this is the first successful coupling of directed *ortho*-metallated dianions with alkoxy-functionalized epoxides. Furthermore, these intermediates are useful precursors for the synthesis of functionalized 3,4-dihydroisocoumarin derivatives, such as AI-77-B (**1**) and apicularen (**2**).

In summary, an effective method for the preparation of synthetically useful 3,4-dihydroisocoumarin derivatives from *t*-butylbenzamides and epoxides was established. Protected glycidols and a homoglycidol were coupled with directed *ortho*-metallated dianions of *t*-butylbenzamides for the first time, and the *t*-butyl amide was readily removed during the lactonization step under acidic conditions.

ACKNOWLEDGEMENTS

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8. *Experimental procedures*: To a solution of **5b** (207 mg, 1.00 mmol) in dry THF (3 mL) were added *n*-BuLi (1.38 mL, 1.6 M in hexanes, 2.20 mmol) and TMEDA (0.33 mL, 2.20 mmol) at –78 ^{o}C under argon. After 2 h, epoxide (**11b**) (243 mg, 1.20 mmol) was added to the dianion solution. The reaction mixture was stirred for 1 h at -78 ^{o}C and 8 h at rt prior to being quenched with saturated aqueous NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (1 x 10 mL) and CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, condensed in reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 4:1 hexane / EtOAc) to give 279 mg of **12e** (68%) as an oil. To a stirred solution of **12e** (113 mg, 0.276 mmol) in THF (3 mL) was added TBAF in THF (0.33 mL, 1.0 M in THF, 0.33 mmol). The mixture was stirred for 1 h at rt, quenched with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (2 x 10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried, condensed in

reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 2% MeOH in CH_2Cl_2) to give 81 mg of **13e** (99%) as an oil. A toluene (4 mL) solution of **13e** (81 mg, 0.273 mmol) and *p*-TsOH • H_2O (52 mg, 0.273 mmol) was refluxed for 2 h. The reaction mixture was condensed under reduced pressure and purified by column chromatography on silica gel (elution with 2% MeOH in CH_2Cl_2) to give 54 mg of **15b** (89 %) as an oil.

9. *Selected spectral data* for **15b**: colorless oil ; R_f = 0.4 (10% MeOH in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$); δ = 7.44 (t, *J* = 8.3 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 4.68-4.57 (m ,1 H), 3.96-3.80 (m, 2 H), 3.92 (s, 1 H), 3.03-2.96 (m, 1 H), 2.87(dd, *J* = 16.3, 3.8 Hz, 1 H), 2.13-1.87 (m, 2 H), 1.83 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.8, 161.3, 142.1, 134.7, 119.4, 113.7, 111.0, 75.5, 58.8, 56.3, 37.3, 34.7; IR (film, cm^{-1}) 3406, 2940, 2889, 2843, 2361, 2341, 1716, 1598, 1481, 1440, 1281, 1245, 1086, 1055, 799, 774, 702; GC-MS: *m/z* (rel. intensity): 77 (30), 90 (60), 105 (40), 129 (25), 148 (100), 177 (65), 193 (30), 222 (M^+, 55).
10. For the alternative synthesis of the known **14b**, see: P. Salvadori, S. Superchi, and F. Minutolo, *J. Org. Chem.*, 1996, **61**, 4190.