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A 6-*exo*-*trig* radical cyclization approach to the hydrochrysene skeleton

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Abstract—The synthetic approach to a functionalized hydrochrysene skeleton is described. The route is highlighted by a Birch reduction–alkylation sequence and a 6-*exo*-*trig* radical cyclization.

The hydrochrysene skeleton is found in many steroidal natural product, as well as a number of alkaloids and terpenoids.[1] Because of the wide occurrence and pharmacological importance of these compounds, the development of a new stereospecific route to access this ring system remains an attractive objective in organic synthesis. Most of the previous syntheses have relied on a cationic cyclization cascade initiated from a polyene precursor for the efficient construction of polycyclic carbocyclic and heterocyclic systems.[2] While this strategy remains extremely powerful for constructing hydrochrysene skeletons, the efficiency of this process depends largely on the suitable choice of an initiator.[3] To complement these traditional methods, a new synthetic alternative which can better accommodate labile functional groups in the substrate during ring formation is desirable.[4] In an ongoing effort directed towards the development of a strategy for the synthesis of natural products containing a hydrochrysene core, we report here a fast and convenient approach to the construction of a functionalized hydrochysene **1** utilizing a low temperature radical cyclization.

Retrosynthetically, we envisaged hydrochrysene **1** (Fig. 1) arising via a 6-*exo*-*trig* radical cyclization of the dienone **2**, which could be prepared from the naphthoate **3**[5] and the allyl bromide **4**[6] via Birch reduction–alkylation.

In practice, the Birch reduction of the naphthoates **3a–c** followed by alkylation with the corresponding allyl bromides **4a–b** provided the dienes **5a–d** in 65–79% overall yield.[7] Oxidation of the dienes **5a–d** at the bis-allylic positions gave the benzo-annulated 2,5-cyclohexadienones **6a–d** in 80–92% yield (Scheme 1).[8]

Our initial investigations on the radical cyclization of the dienones **6** were carried out under standard condi-

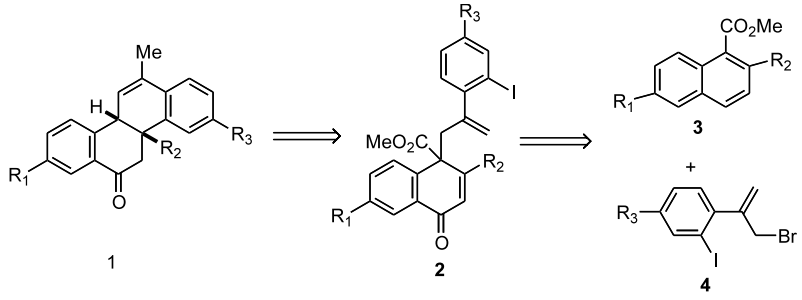

Figure 1.

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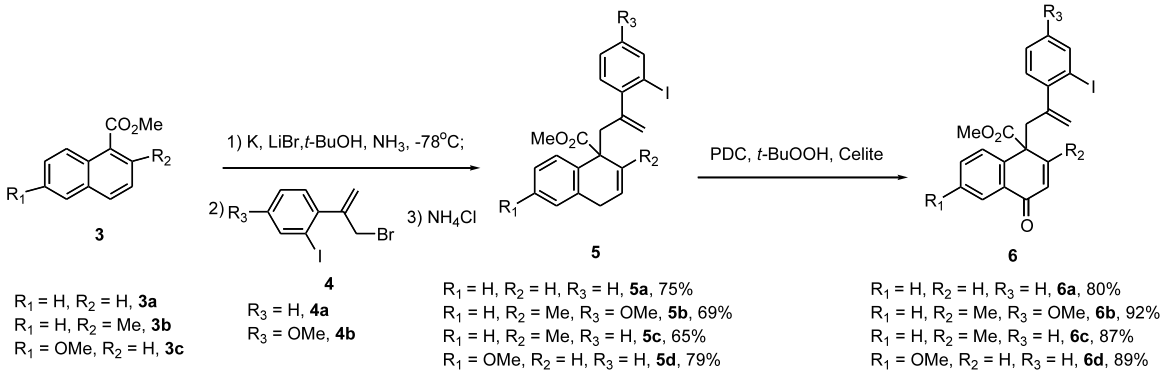


Scheme 1.

tions with Bu_3SnH, Ph_3SnH or $(TMS)_3SiH$ and AIBN as an initiator at 80°C in benzene over 2 h. Unfortunately, the only products obtained under these conditions were the doubly-cyclized adducts **7b–c** resulting from a 6-*exo*-*trig* followed by 5-*exo*-*trig* cyclization[9] (Scheme 2). We reasoned that since the first 6-*exo*-*trig* cyclization should occur much more rapidly than the second 5-*exo*-*trig* cyclization, lower temperatures would allow for the reduction of the intermediate radical species immediately following the first 6-*exo*-*trig* radical cyclization thereby eliminating the by-product arising from tandem cyclization.

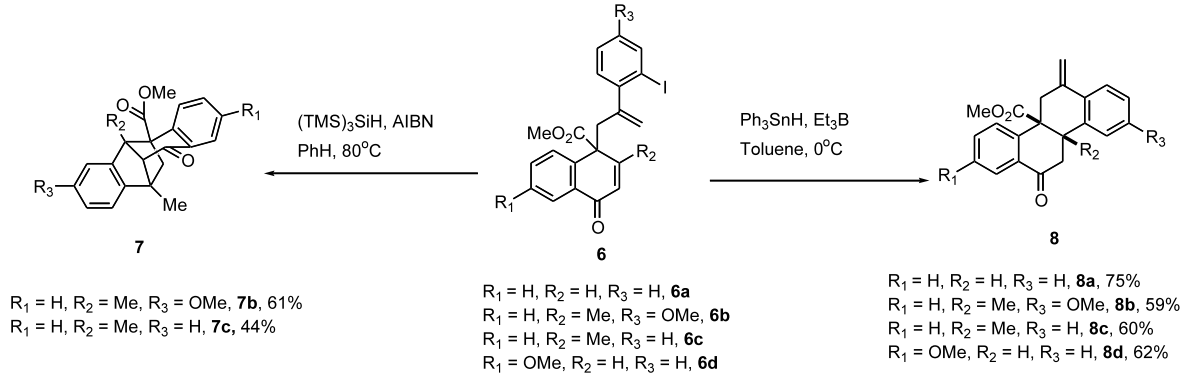
There is much precedence for the use of stoichiometric Ph_3SnH with Et_3B as the initiator for low temperature radical cyclizations.[10] Applying these conditions to our system, we were pleased to find that the cyclohexadieones **6a–d** smoothly cyclized to give **8a–d** as the major products.[11] The results of the temperature effect on this cyclization are summarized in Table 1. At −78°C, the radical cyclization cleanly gave the desired hydrochrysene derivative **8b** with some starting material remaining. At higher temperatures, as expected, the ratio of the by-product **7b** to the desired product **8b** increased. Ultimately, we found that the optimal temperature for the formation of the desired **8b** was 0°C.

Compound **8b** could be further transformed into the key intermediate **10**, which constitutes a hydrochrysene skeleton such as **1**. Thus, isomerization of the *exo* double bond of **8b** to the thermodynamically more stable *endo* double bond was accomplished by treatment with $RhCl_3 \cdot H_2O$ in EtOH in 92% yield (Scheme 3). Decarboxylation of **9** under thermodynamical control with LiI in collidine afforded the adduct **10** as a single diastereomer in 64% yield, along with its regioisomers **11** as minor by-products (~17%).[12] The *cis* ring junction of the hydrochrysene derivative **10** was assigned based on molecular modeling studies and confirmed by NOE studies. Molecular mechanics, semi-empirical and ab-initio calculations using Spartan software calculated the *cis* isomer **10** to be thermodynamically more stable [ΔE (E_{cis}–E_{trans}) = −5.01 kcal/mol, MMFF; ΔE = −2.30 AM1; ΔE = −3.03, 31G**) than its corresponding *trans* isomer. An NOE between the angular H at δ 3.99 and the angular CH_3 at δ 0.96 confirmed the *cis* ring junction of **10**.

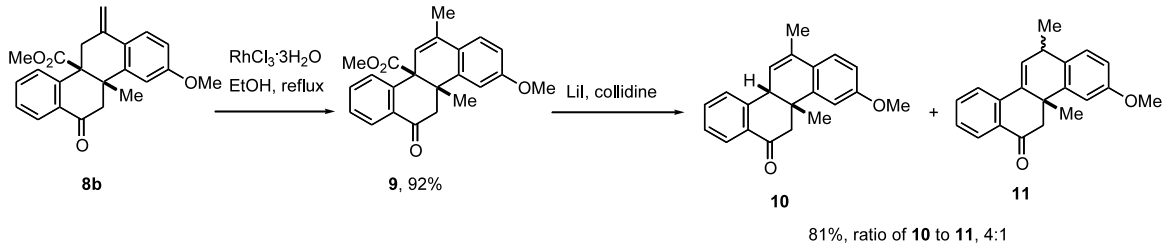
Table 1. Temperature effect on transformation of **6b** to **7b** and **8b**[a]

Reaction temp. (°C)	**6b** (%)	**7b** (%)	**8b** (%)
−78	33	0	67
−10	10	5	85
0	0	10	90
25	0	20	80

[a] The percentage of **6b**, **7b** and **8b** was calculated from integration of CO_2-Me groups on ^1H NMR.



Scheme 2.



Scheme 3.

In conclusion, a sequential Birch reduction–alkylation and 6-*exo*-*trig* radical cyclization approach to the hydrochrysene skeleton has been developed resulting in the efficient synthesis of several versatile intermediates. Further exploration of this methodology will be reported in due course.

Acknowledgements

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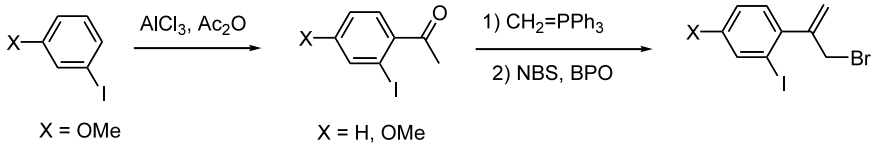
5. Synthesis of the alkylating agents:



6. Compound **3a** and **3b** were prepared from 1-bromonaphthalene and 1-bromo-2-methylnaphthalene by carboxylation and esterification. For the preparation of **3c**, see: Bright, J. H. US Patent 4,590,290, 1986.
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9. *Preparation of* ***7c***. A solution of $(TMS)_3SiH$ (0.02 mL, 0.065 mmol) and AIBN (2 mg) in deoxygenated PhH (0.5 mL) was added dropwise via syringe pump over 30 min to the dienone **6a** (25 mg, 0.056 mmol) and AIBN (2 mg) in PhH (5 mL) at reflux. The solution was refluxed for an additional 2 h. The solvent was removed in vacuo and the residue was purified by flash chromatography using 4:1 hexanes: EtOAc as eluent to give **7c** as a white solid (8.0 mg, 44% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, $J=7.8$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H), 7.40 (t, $J=7.6$ Hz, 1H), 7.28–7.25 (m, 1H), 7.20–7.19 (m, 3H), 7.08 (d, $J=7.6$ Hz, 1H), 3.67 (s, 3H), 2.78 (s, 1H), 2.62 (d, $J=13.0$ Hz, 1H), 1.95 (d, $J=13.0$ Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 196.8, 172.6, 151.0, 148.3, 144.4, 133.7, 131.4, 127.6, 127.5, 127.0, 126.1, 124.9, 121.1, 118.0, 77.7, 62.1, 60.3, 53.1, 51.8, 47.6, 14.1, 13.0.
10. For a low temperature radical cyclization initiated by Et_3B, see: (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547; (b) Satoh, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 2278; (c) Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692.
11. *Preparation of* ***8b***. To a solution of **6b** (59 mg, 0.122 mmol) and Ph_3SnH (64 mg, 0.182 mmol) in distilled toluene (15 mL) at 0°C was added dropwise Et_3B (134 μL of 1.0 M solution in hexane, 0.134 mmol). The resulting solution was stirred for 2 h at 0°C, warmed to room temperature and quenched with saturated NH_4Cl. The reaction mixture was diluted with EtOAc, partitioned between water and EtOAc, and aqueous layer was extracted with EtOAc(2×). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude product. Flash chromatography purification using 4:1 hexanes: EtOAc as eluent afforded **8b** as a

white solid (31 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, $J=7.8$ Hz, 1H), 7.62 (d, $J=7.9$ Hz, 1H), 7.41 (m, 1H), 7.35 (m, 2H), 6.85 (s, 1H), 6.61 (d, $J=8.3$ Hz, 1H), 5.24 (s, 1H), 4.83 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.57 (d, $J=18.6$ Hz, 1H), 3.47 (d, $J=15.5$ Hz, 1H), 3.31 (d, $J=15.7$ Hz, 1H), 3.21 (d, $J=18.6$ Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 196.0, 173.3, 159.7, 141.3, 138.1, 133.3, 128.1, 127.4, 127.0, 126.6, 12.8, 125.3, 112.5, 111.7, 108.8, 55.0, 53.9, 52.3, 47.6, 43.5, 40.6, 28.6. IR (film, cm^{-1}) 1726, 1691. CIMS 363 (M^++1, 100).

12. *Selected data for* ***10***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, $J=7.8$ Hz, 1H), 7.71 (d, $J=7.8$ Hz, 1H), 7.65 (t, $J=7.4$ Hz, 1H), 7.41 (t, $J=6.9$ Hz, 1H), 7.33 (d, $J=8.3$ Hz, 1H), 6.85 (s, 1H), 6.81 (d, $J=7.6$ Hz, 1H), 6.22 (s, 1H), 3.99 (s, 1H), 3.85 (s, 3H), 3.31 (d, $J=16.4$ Hz, 1H), 2.98 (d, $J=16.4$ Hz, 1H), 2.21 (s, 3H), 0.96 (s, 3H). CIMS 305 (M^++1, 100). Anal. calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.75; H, 6.68%.