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Short Research Article

Synthesis of ($^{13}C_6$-Ring-(U))-(±)-benzo(*a*)pyrene metabolites from ($^{13}C_6$-Ring-(U))benzene†

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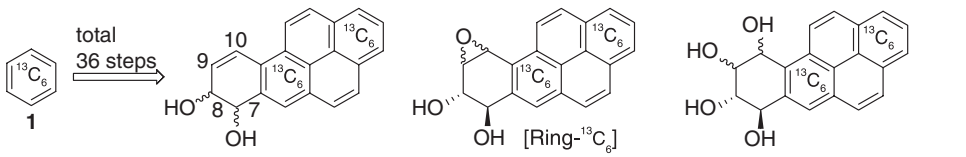
Introduction

Benzo[*a*]pyrene, B[*a*]P, is one of the most potent and most prevalent environmental procarcinogens. The B[*a*]P metabolites, e.g. the diols **2**, diol-epoxides **3** and tetrols **4**, appear to be the ultimate carcinogenic derivatives. To facilitate research in the mechanisms of carcinogenesis/mutagenesis by such compounds, stable isotope-labeled analogs are valuable aids for mass spectrometric analysis. An efficient synthetic route utilizing Suzuki-coupling chemistry provided isotopomeric [$^{13}C_6$-1,2,3,3a,10a,10b]-pyrene **18**, which served as the central intermediate for subsequent production of the $^{13}C_6$-ring-labeled diols **2**, diol-epoxides **3**, and tetrols **4**.

Results and discussion

To our knowledge, there have been no previous reports of a simple and efficient method to introduce a [$^{13}C_6$-Ring-(U)] into pyrene **13**, especially for the purpose of producing [$^{13}C_6$-Ring-(U)]-labeled benzo[*a*]pyrenes and/or any of the associated metabolites. In order to obtain the target benzo[*a*]pyrene metabolites, we have designed and successfully executed a new synthetic route for this purpose. This new strategy is summarized in Schemes 1 and 2.

[Ring-$^{13}C_6$ (U)]-benzene **1** was selected as the basic building block and successfully incorporated into the key intermediate **18**, 9,10-dihydrobenzo[*a*]pyrene, via [$^{13}C_6$-1,2,3,3a,10a,10b]-pyrene **13**, via a Suzuki-coupling reaction of the diformyl aryl bromide **9** and phenylboronic acid **6**.[1,2] The diformyl biaryl **10** was converted to the bis(2-methoxyvinyl) compound **11**, which upon acidic hydrolysis and ring closure provided [$^{13}C_6$-Ring-(U)]-pyrene **13**. The pyrene core was subsequently elaborated to the isotopomeric [$^{13}C_6$-Ring-(U)]-9,10-dihydrobenzo[*a*]pyrene **18** via standard Friedel–Crafts methodology.[3,4] The (±)-*trans*-dihydrodiol **19**



(±)-**2**a:7β, 8α
(±)-**2**b:7β, 8β

(±)-**3**a:9β, 10β
(±)-**3**b:9α, 10α

(±)-**4**a:9α, 10α, (±)-**4**b:9α, 10β
(±)-**4**c:9β, 10α, (±)-**4**d:9β, 10β

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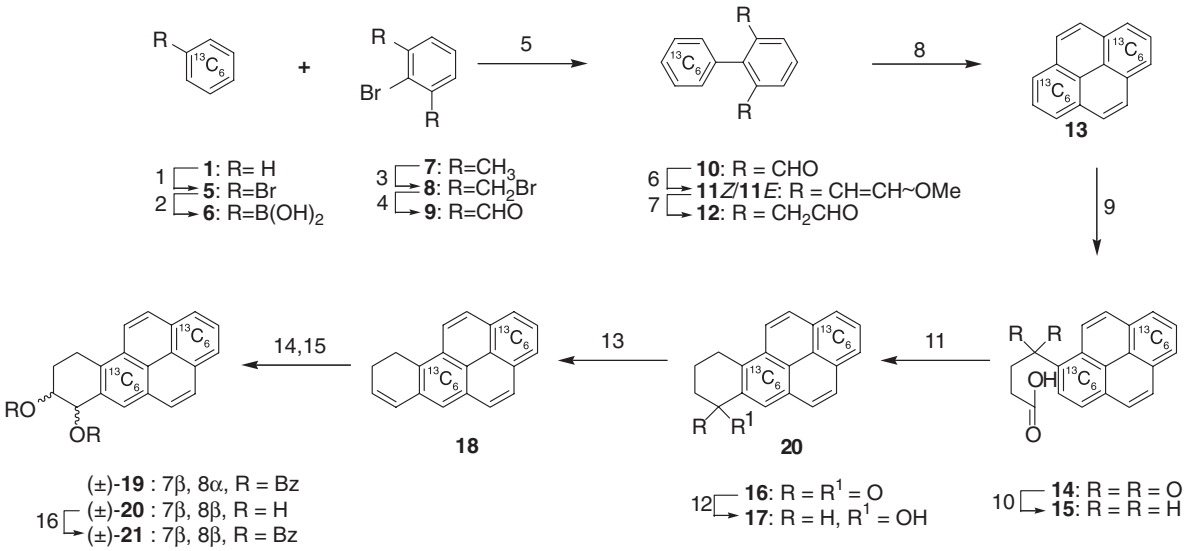

Reagents and conditions: (1) 1,3-Dibromo-5,5-dimethylhydantoin, CH_2Cl_2, F_3CSO_3H, 70%; (2) (i) Mg, ether, (ii) $B(OEt)_3$, ether, 100%; (3) NBS, AIBN, benzene, external 85W UV lamp, 92%; (4) 88% formic acid, reflux, 99%; (5) $Pd(PPh_3)_4$, DME, H_2O, Na_2CO_3, reflux, 90%; (6) (i) **6**, $MeOCH_2P(Ph_3)$, ether, *t*-BuOK, (ii) **9**, THF, 96%; (7) 6N HCl, H_2O, acetone, 100%; (8) 10% F_3CCOOH in CH_2Cl_2, 87%; (9) Succinic anhydride, nitrobenzene, $AlCl_3$, 92%; (10) Zn–Hg, HCl, Chlorobenzene, xylene, reflux, 100%; (11) (i) PCl_5, benzene, (ii) $SnCl_4$, 98%; (12) $NaBH_4$, EtOH, 70%; (13) HOAc, conc. HCl, reflux, 100%; (14) for **19**, 89%: (i) AgOBz, I_2, benzene, (ii) added **18**, reflux; (15) for **20** Acetone, *N*-methyl-morpholine-*N*-oxide, H_2O, OsO_4, 49%; (16) Pyridine, benzoylchloride, 86%.

Scheme 1

and (±)-*cis*-dihydrodiol **20**, protected as their respective benzoates, were accessed by reaction of **18** with either silver benzoate/iodine or osmium tetroxide followed by benzoyl chloride, respectively.[5,6]

The double bond between C-9 and C-10 of (±)-**22** or (±)-**23** was introduced by the reaction of (±)-**19** or (±)-**21** with DDQ, followed by base hydrolysis to afford the *trans*- and *cis*-dihydrodiols (±)-**2**a or (±)-**2**b, respectively (Scheme 2). The (±)-*anti*-**3**b, (9α,10α), was synthesized directly from the dihydrodiol **2**a by oxidation with 3-chloroperoxybenzoic acid (MCPBA). The corresponding (±)-*syn*-**3**a was accessed via the intermediate bromide (±)-**26**, which was obtained via the bromohydrin **26** with *N*-bromoacetamide in the presence of catalytic conc. HCl(aq), and subsequent elimination using ion-exchange resin (base form).

Tetrol (±)-**4**b was prepared by the same procedure described for preparing (±)-**20**, with the addition of a basic ester hydrolysis (step 22), acetylation using acetic anhydride/pyridine (step 23), and subsequent acetate hydrolysis (step 24), all for the purpose of facilitating efficient purification of the desired tetrol. The remaining three tetrols, (±)-**4**c, (±)-**4**d and (±)-**4**a, were prepared from diol epoxides (±)-**3**a or (±)-**3**b by acidic or base peroxide ring opening.[7] Purification of the tetrols (±)-**4** is an especially challenging aspect of this chemistry. Fortunately, the purification of these interesting products was resolved by repeating the hydroxyl acetylations and base hydrolyses, as well as via recrystallization.

Conclusion

A new facile and efficient synthetic method was designed and developed for preparing benzo[*a*]pyrene diols. By this synthetic strategy, eight metabolites, diol: (±)**2**a, (±)**2**b, diol-epoxides: (±)**3**a, (±)**3**b, tetrols: (±)**4**a, (±)**4**b, (±)**4**c and (±)**4**d were synthesized successfully by 36 steps totally.

REFERENCES

1. Zippi EM. *J Label Compd Radiopharm* 2001; **44**: 757.
2. Wu Y, Yang L, Zhang J, Wang M, Zhao L, Song M, Gong J. *ARKIVOC* 2004; **9**: 111.
3. (a) Fuson RF, Scott SL, Lindsey RV. *J Am Chem Soc* 1941; **63**: 1679; (b) Bachmann WE, Carmack M, Safir SR. *J Am Chem Soc* 1941; **63**: 1682; (c) Fieser LF, Novello FC. *J Am Chem Soc* 1940; **62**: 1855.

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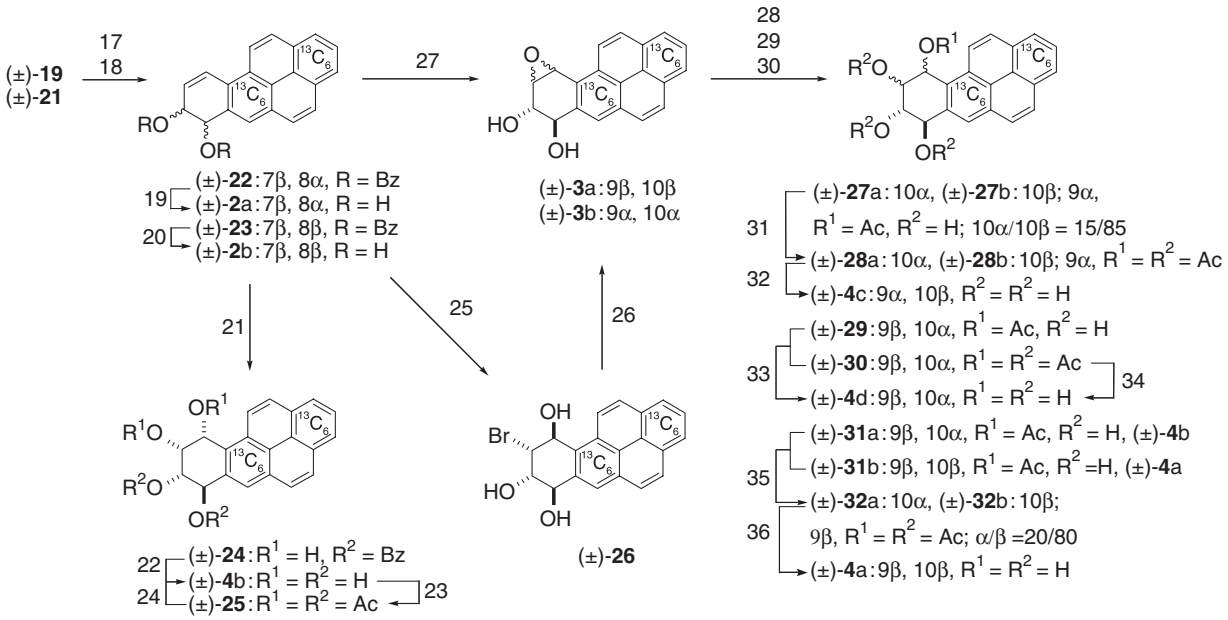

Reagents and conditions: (17) for **22**, DDQ, 1,4-dioxane, reflux, 93%; (18) for **23**, DDQ, benzene, reflux, 41%; (19) NaOMe, MeOH, reflux, 94%; (20) K_2CO_3, MeOH, THF, 75%; (21) OsO_4, pyridine, 72%; (22) 10% NaOH, THF, 89%; (23) Ac_2O, Py, 86%; (24) 10% NaOH, THF, 63%; (25) *N*-bromo-acetamide, THF, H_2O, conc. HCl aq, 94%; (26) for **3**a, THF, Amberlite ®IRA-400 ·OH, 76%; (27) for **3**b, MCPBA, THF, 91%; (28) for **32**, AcOH, H2O, 1,4-dioxane, 85%; (29) for **29** ,KOAc, dibenzo-18-crown-6, acetonitrile, 89%; (30) for **31**, AcOH, H2O, 1,4-dioxane; (31) Ac2O, pyridine, 99%; (32) 20% NaOH, THF, 97%; (33) Ac2O, pyridine, 25%; (34) 10% NaOH, THF, 83%; (35) Ac2O, pyridine, 43% from **3**a through step 30; (36) 10% NaOH, THF, 43%.

Scheme 2

4. Klassen SE, Daub GH, VanderJagt DL. *J Org Chem* 1983; **48**: 4361.
5. Kumar S, Panna LK, Sehgal RK. *J Org Chem* 1989**;** **54**: 5272.
6. Fu PP, Harvey RG. *Tetrahedron Lett* 1977; **24**: 2059.
7. Yagi H, Thakker DR, Hernandez O, Koreeda M, Jerina DM. *J Am Chem Soc* 1977; **99**: 1604.

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