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Short Research Article

Labeling strategies of selected subtypes of the hexahydro-naphth[2,3-b]-1,4-oxazine- and octahydrobenzo[*g*]quinoline-type†

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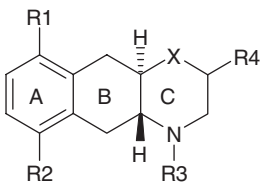
Introduction

A class of compounds characterized by the structure below showed therapeutic value in the treatment of CNS disorders.[1a,1b,1c] Some selected candidates demonstrated that a variety of labeling strategies needed to be developed in order to meet particular requirements of specific activity, position of label, metabolic stability and starting material.



Results and discussion

Strategy A: Formation of the ring C starting from [^{14}C]chloroacetyl chloride (Scheme 1).

Strategy B: Tritiation of an unsaturated precursor (Scheme 2).

Strategy C: Reduction of β-keto ester with Cp_2ZrCl^3H (Schwartz's reagent)[2a,2b] (Scheme 3).

Since the stereochemistry of the ^{3}H-label is governed by the reduction of the double bond, reduction with T_2 (Strategy B) and reduction with H_2 (Strategy C) produce complementary isotopomers (**2B** versus **3B**).

Strategy D: C-14,C-13,H-2-Labeling of **4B/C** by selective degradation/resynthesis approach (Scheme 4).

In this specific case the –Si–CH_3 (as well as the O–CH_3 and the N–CH_3) moiety was found to be

Type	No.	R^1	R^2	R^3	R^4	X	Label
I	1A	–SCH_3	–OCH_3	–CH_3	–H	–O	C-14
II*	2B	–OH	–H	–C_3H_7	–$NHSO_2NEt_2$	–CH_2	H-3
III	3B	–OH	–H	–CH_3	–CH_2–S–R	–CH_2	H-3
IV	4A	–$Si(CH_3)_3$	–OCH_3	–CH_3	–H	–CH_2	C-14 (ring)
	4B	–$Si(^{13}CD_3)(CH_3)_2$					C-13,H-2
	4C	–$Si(^{14}CH_3)(CH_3)_2$					C-14

*Antipode of the structure given above.

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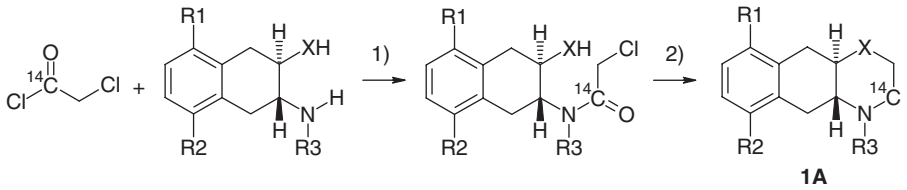
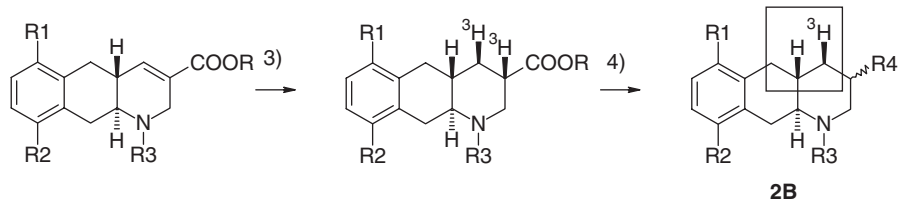
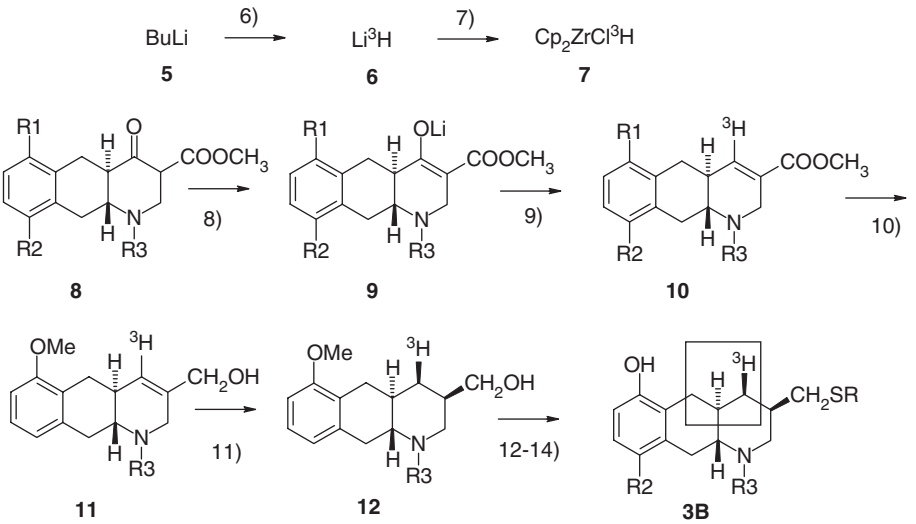


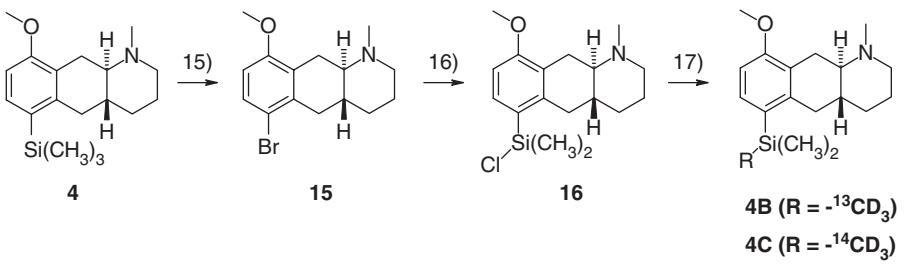
Scheme 1 Reaction conditions: (1) NEt_3, CH_2Cl_2, 25°C, 16 h; (2) NaH, Bu_4NI, THF, 25°C, 16 h.



Scheme 2 Reaction conditions: (3) $^3H_2$, Raney-Ni, CH_3OH, 25°C, 1 h; (4) LDA, THF, −35°C, 0.5 h, H_2O, H^+.



Scheme 3 Reaction conditions: (6) Cp_2Zr^3H: T_2, *n*-BuLi, TMEDA, THF; (7) THF, Cp_2ZrCl_2; (8) LDA, THF; (9) **7**, THF, −20°C; (10) $LiAlH_4$, THF, −20°C, 1 h, 20°C; (11) H_2, Pd/C 10%, EtOH, 4 h, 20°C; (12) methanesulfonyl chloride, pyridine, 3 h, 20°C; (13) 2-mercapto-derivative in DMF, 4 N NaOH, DMF, 2 h, 20°C; (14) BBr_3 in CH_2Cl_2, 2 h, 20°C.



Scheme 4 Reaction conditions: (15a) 0.2 N HCl, 80°C, 95%, (b) Br_2, CCl_4, 58%; (16) *tert*-BuLi, THF, −78°C, 1 h, 0°C, $Cl_2Si(CH_3)_2$, 2 h (not isolated); (17) Synthesis of $^{13}C^2H_3Li$ (resp. $^{14}CH_3Li$): $^{13}C^2H_3I$ (resp. $^{14}CH_3I$), *tert*-BuLi (1.5 M in pentane), −78°C, Et_2O, 15 min, RT; addition, 52% (related to **15**).

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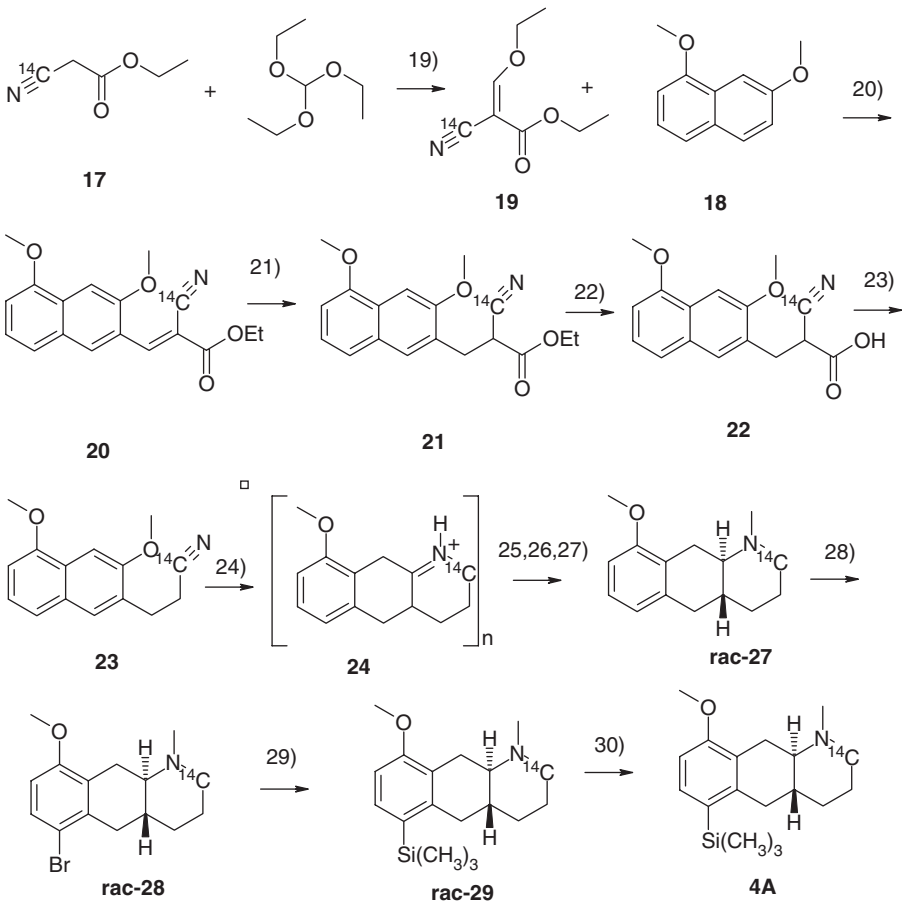

Scheme 5 Ring C C-14 labeling using a sequential, multi-step strategy. Reaction conditions: (19) acetic anhydride, 145°C, 5 h, flash-chromatography, 74%; (20), *n*-BuLi, THF, −20°C, −70°C, 1 h, −25°C, H_2SO_4, not isolated; (21) Pd/C 5%, THF/EtOH, H_2, 25°C, 22 h, flash-chromatography, 46%; (22) NaOH, EtOH, 90°C, 3 h, 96%; (23) *N,N*-dimethylacetamide, NaCl, H_2O, 150°C, 2.5 h, not isolated; (24) Na-metal, *n*-butanol, 90°C, 3 h, HCl-H_2O, not isolated; (25) $NaBH_4$, *n*-butanol, EtOH, acetic acid, water, not isolated; (26) formaldehyde, $NaCNBH_3$, EtOH, 25°C, 0.5 h; (27) separation of the *cis*/*trans* isomers by flash-chromatography, 42% related to **22**; (28) HBr, $HBrO_3$, acetic acid/water 1:1, flash chromatography, 94%; (29) *n*-BuLi, trimethylsilyl chloride, THF, flash-chromatography, 88%; (30) separation of the antipodes by preparative HPLC-chromatography, 48%.

metabolically unstable and thus a strategy for ring-labeling had to be developed.[3]

Strategy E: Ring C C-14 labeling using a sequential, multi-step strategy (Scheme 5).

Regio-, diastereo- and enantioselective challenges of this route are addressed using an optimized procedure.[4] Key-steps are the regioselective *ortho*-lithiation of **18** with subsequent Michael addition of the bulky acceptor **19** (step 20) and the simultaneous reduction of the methoxynaphthalene moiety and the nitrile function resulting in the cyclic enamine **24** (step 24). Final separation of the enantiomers was accomplished by chiral preparative HPLC-purification (step 30), however, larger quantities might be separated by recrystallization with (-)-*o,o*-ditoluoyl-L-tartaric acid.

Conclusion

Based on particular requirements a broad variety of strategies were applied to label the class of title compounds. Particularly, in those cases which provided the β-keto ester as starting material the introduction of the 3H-label by the 'tritio-zirconation' approach (Strategy 3) was most successful, resulting in isotopomers of high specific activity. Since the degradation/resynthesis approach of **4** provided labeling in a metabolically unstable position a total synthesis was inevitable. At a first glance the multi-step-synthesis appeared undesirable, especially due to regio-, as well as diastereo- and enantioselective problems. However, taking advantage of the already

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optimized procedures subsequent application to isotope-labeling was attractive.

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