Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 688–695
www.elsevier.com/locate/tet

A versatile method for the hydrolysis of *gem*-dibromomethylarenes bearing carboxylate or boronate group into aldehydes

John Kallikat Augustine [a,*], Y. Arthoba Naik [b], Ashis Baran Mandal [a], Nagaraja Chowdappa [a], Vinuthan B. Praveen [a]

[a] *Syngene International Ltd, Biocon Park, Plot Nos. 2 and 3, Bommasandra-Jigani Road, Bangalore 560 100, Karnataka, India*
[b] *Department of Studies in Chemistry, Kuvempu University, Shankaraghatta, Shimoga 577 451, Karnataka, India*

Received 8 August 2007; received in revised form 27 October 2007; accepted 8 November 2007
Available online 12 November 2007

Abstract

Hydrolysis of *gem*-dibromomethylarenes bearing carboxylate or boronate group to corresponding aldehydes without affecting the ester group was successfully accomplished in high yields by subjecting them to refluxing pyridine. Both aromatic and heteroaromatic substrates gave the corresponding aldehydes in good yields. This method was efficiently adapted for the large scale synthesis of **2d** and **2f**.

Keywords: *gem*-Dibromomethylarene; Hydrolytic; Bis-pyridinium cation; Heteroaromatic; Boronate

1. Introduction

In an ongoing project we desired the large scale synthesis of various heteroaromatic carboxylates bearing a reactive aldehyde group. The simple and ready availability of starting materials prompted us to explore the synthesis of these aldehydes via a two-step protocol wherein the commercial methyl analogues are first converted to their *gem*-dibromomethyl intermediates and further hydrolysis of these intermediates to aldehydes. Functional group transformation of *gem*-dihalo compounds to aldehydes is a widely used method for the synthesis of aldehydes.[1] This transformation requiring hydrolysis of a *gem*-dibromomethyl group to an aldehyde often employs harsh reaction conditions such as use of H_2SO_4,[2] aqueous sodium hydroxide[3] and metal carbonates[4] at high temperatures. When we attempted the hydrolysis of these *gem*-dibromomethyl intermediates under the above mentioned methods, the simultaneous hydrolysis of ester functionality took place. The use of mild reagent such as aqueous dimethylamine[5] afforded mixtures of products due to the amidation of the ester group with the amine, while aqueous $AgNO_3$[6] and sodium acetate in acetic acid[7] in our hands failed to afford good yield of these aldehydes except **2d**. Aqueous sodium formate,[8] aqueous potassium oxalate[9] and water[10] were found to be ineffective in hydrolyzing the *gem*-dibromides even at high temperatures. All the above mentioned methods were invariably associated with certain limitations in terms of acid/base conditions, high temperatures, poor yields or substrate scope. An extensive search in the literature revealed the lack of rigorous methodology in this area, particularly for substrates containing acid-sensitive functional groups. However, there are isolated examples wherein, aqueous silver nitrate[6] is reported to effect this transformation. This emphasizes the need of a general pathway for hydrolyzing *gem*-dibromomethylarenes bearing ester functionality without affecting the ester group.

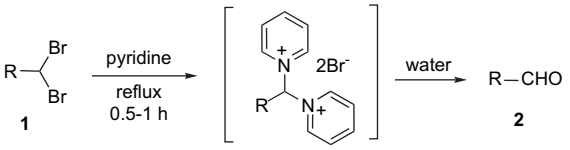
2. Synthetic plan

As our attempts to hydrolyze selectively the *gem*-dibromide were futile, we looked for alternative protocols. Our attention then turned to a report by Kröhnke[11] on the transformation of benzal bromide to a reasonably stable bis-pyridinium cation. Kröhnke has shown that the bis-pyridinium cation of benzal

* Corresponding author. Tel.: +91 80 2808 3131; fax: +91 80 2808 3150.
E-mail address: john.kallikat@syngeneintl.com (J.K. Augustine).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.11.030

bromide is slowly hydrolyzed in water to benzaldehyde and pyridine (Scheme 1). Interestingly, this method has not been exploited for the transformation of *gem*-dihalomethyl compounds to aldehydes and its broad scope in synthetic chemistry for the specific hydrolysis of *gem*-dibromomethylarenes to aldehydes has not been studied. However, Olofson and Zimmerman reported the use of bis-pyridinium cation in the synthesis of 1-deuterio aldehydes.[12] Thus we decided to explore the synthesis of these aldehydes via their bis-pyridinium intermediate.



R = aryl or heteroaryl molecules substituted with a carboxylate or boronate group

Scheme 1.

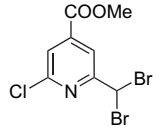
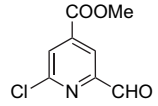
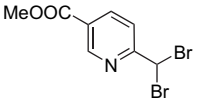
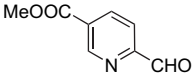
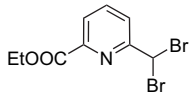
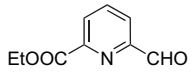
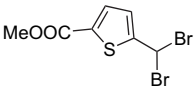
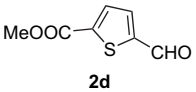
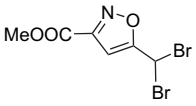
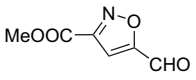
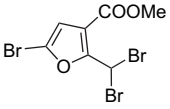
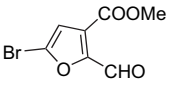
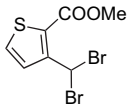
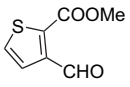
3. Results and discussion

Initially, we examined the synthesis of **2a** by treating its precursor **1a** with pyridine. Use of 2 equiv of anhydrous pyridine did not afford complete conversion of **1a** to its bis-pyridinium cation even after 20 h at 100 °C as indicated by TLC. The reaction was then screened with varying equivalents of pyridine at 100 °C. When 7 g of **1a** was exposed to excess of pyridine at reflux (10 equiv), the starting material was completely consumed in 80 min as confirmed by TLC.[13] Further increases in the quantity of pyridine or increase in the reaction temperature did not lower the reaction time. This intermediate was found to be highly sensitive to moisture and all our attempts of isolating it in pure form were not successful, rather we ended with **2a**. Once the reaction was complete as indicated by TLC, the brown reaction mass was exposed to cold water to liberate the aldehyde. The product was extracted with ether to afford **2a** in 73% isolated yield (Entry 1, Table 1).

Encouraged by this success, the other heteroaromatic *gem*-dibromomethyl compounds bearing ester functionality (Entries 2–7, Table 1) such as pyridine, thiophene, furan and isoxazole were subjected to refluxing anhydrous pyridine as shown in Scheme 1. The results were excellent as depicted in Table 1. With this optimized reaction conditions we were able to transform 78 g of **1a** into **2a** with an isolated 70% yield. Similarly, 190 g of **1d** afforded **2d** in 76% yield (Entry 4, Table 1) and 367 g of **1f** afforded **2f** in 87% isolated yield (Entry 6, Table 1). This illustrates the potential use of this method in scale-up operations.

In order to generalize this methodology, we then applied the optimized reaction conditions on various aromatic *gem*-dibromides substituted with a carboxylate group. To our delight, all the *gem*-dibromides provided high yields of corresponding aldehydes and the reaction time was short as illustrated in Table 2. In addition, the hydrolysis of *gem*-dibromides bearing a boronate group (Entries 1–3, Table 3) was also investigated.

Table 1
Hydrolysis of heteroaromatic *gem*-dibromomethyl intermediates bearing carboxylate group into aldehydes via Scheme 1

Entry	Substrate[a]	Time (min)	Product	Yield[b] (%)
1	 **1a**	80	 **2a**	73
2	 **1b**	90	 **2b**	72
3	 **1c**	80	 **2c**	77
4	 **1d**	70	 **2d**	76
5	 **1e**	90	 **2e**	72
6	 **1f**	80	 **2f**	87
7	 **1g**	70	 **2g**	91

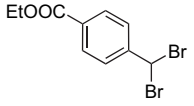
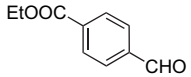
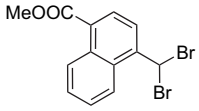
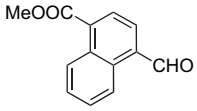
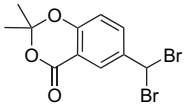
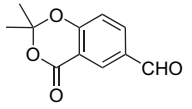
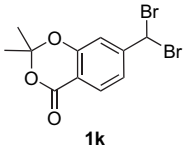
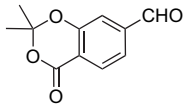
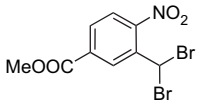
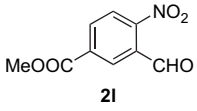
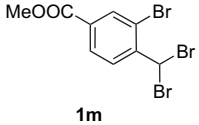
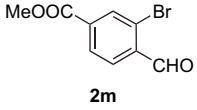
[a] Substrates were synthesized from the corresponding methyl analogues by radical bromination.[18]
[b] Isolated yields.

The boronate group survived during the course of reaction and provided the corresponding aldehydes in high yields.

Effect of solvents on the rate of hydrolysis of **1a** was studied and the results are shown in Table 4. While the reaction of **1a** with pyridine (10 equiv) in dioxane afforded 31% of **2a**, which in toluene afforded 28% yield after 12 h at 100 °C and DMF gave 44% of the product. Similarly the reaction was found to be very slow in ethylene dichloride and a combination of water and pyridine (Entry 6, Table 4) did not show any reaction even after 15 h at reflux. It is noteworthy that the reaction of **1a** with pyridine in methanol (Entry 7, Table 4) gave only the dimethyl acetal of **2a** in 56% yield. Neat anhydrous pyridine (Entry 1, Table 4) was found to be the most suitable reaction medium to afford the product in 73% yield in short time.

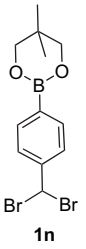
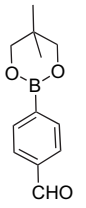
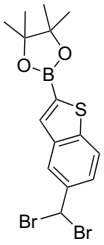
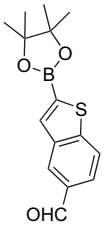
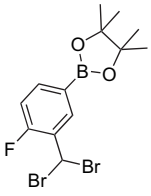
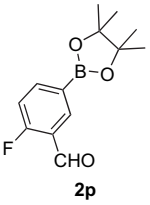
Herein, we report a general approach to transform *gem*-dibromomethylarenes bearing ester functionality to corresponding aldehydes without affecting the ester group in high yields

Table 2
Hydrolysis of aromatic *gem*-dibromomethyl intermediates bearing carboxylate group into aldehydes via Scheme 1

Entry	Substrate	Time (min)	Product[a]	Yield[b] (%)
1	 **1h**	60	 **2h**	81
2	 **1i**	90	 **2i**	90
3	 **1j**	60	 **2j**	79
4	 **1k**	60	 **2k**	87
5	 **1l**	70	 **2l**	90
6	 **1m**	70	 **2m**	89

[a] Products were characterized by NMR spectral analysis.
[b] Isolated yields.

Table 3
Hydrolysis of *gem*-dibromomethylarenes bearing boronate group into aldehydes via Scheme 1

Entry	Substrate[a]	Time (min)	Product	Yield[b] (%)
1	 **1n**	90	 **2n**	93
2	 **1o**	100	 **2o**	89
3	 **1p**	90	 **2p**	83

[a] Substrates were prepared from commercially available methyl analogues by radical bromination.[18]
[b] Isolated yields.

by exposing them to pyridine at reflux for 0.5–1 h. This transformation is believed to proceed via the bis-pyridinium cation[14] as cited by Kröhnke and considerably exceeds previous methods with respect to its generality and simplicity when a carboxylate or boronate group is present on the substrate. Pyridine being a mild base and better solvent, unlike other hydrolytic conditions, the carboxylate and boronate groups survived during the course of reaction and afforded high yields in short time. It is noteworthy that heteroaromatic *gem*-dibromides bearing an ester functionality, for example, pyridine (Entries 1–3, Table 1), thiophene (Entries 4 and 7, Table 1), isoxazole (Entry 5, Table 1) and furan (Entry 6, Table 1) reacted smoothly with pyridine to afford the corresponding aldehydes in excellent yields.

4. Conclusion

In summary, a convenient and versatile method has been demonstrated for the specific hydrolytic conversion of *gem*-dibromomethylarenes substituted with carboxylate or boronate functionality into the corresponding aldehydes without affecting the ester group in respectable isolated yields. The method developed is mild and gave good yields of aldehydes for both aromatic and heteroaromatic substrates and can be conveniently adapted for large scale synthesis of such aldehydes.

Table 4
Hydrolysis of **1a** using pyridine (10 equiv) in the presence of various solvents at 100 °C

Entry	Solvent	Time (h)	Yield[b] (%)
1	Pyridine[a]	1.3	73
2	1,4-Dioxane	12	31
3	Toluene	12	28
4	Ethylene dichloride	15	9[c]
5	DMF	12	44
6	Water	15	NR[d]
7	Methanol	20	56[c,e]

[a] Neat pyridine (10 equiv) was used.
[b] Isolated yields.
[c] Reaction was carried out at 80 °C.
[d] No reaction.
[e] Isolated as dimethyl acetal of **2a**.

5. Experimental section

5.1. General

^{1}H and ^{13}C NMR spectra were recorded on 400-MHz and 100-MHz Bruker spectrometer, respectively, and elemental

analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Melting points were recorded (uncorrected) on Buchi Melting Point B-545 instrument. Coupling constants were reported wherever it was necessary in Hertz (Hz). Reactions were carried out in an oven dried three-necked round-bottomed flask. Yields in table refer to isolated yields of compounds with purity >95% as determined by ^{1}H NMR and HPLC analysis. Compounds previously described in the literature were characterized only by ^{1}H and ^{13}C NMR.

All *gem*-dibromomethyl compounds were synthesized and purified in-house from the corresponding commercially available methyl analogues following reported literature.[15] Substrates **1j** and **1k** were synthesized from 2,2,6-trimethyl-benzo[1,3]dioxin-4-one[16] and 2,2,7-trimethyl-benzo[1,3]-dioxin-4-one.[17] The methyl analogues of **1o** and **1p** were obtained from the commercial boronic acids by treating with pinacol (1.1 equiv) in toluene. All the new substrates were easily prepared and characterized from the corresponding methyl analogues using radical bromination at reflux. Use of 2 equiv of *N*-bromosuccinimide was found to be optimal for the complete dibromination.[18] Aldehydes **2a**, **2f**, **2j**, **2k**, **2o** and **2p** are new and characterized by IR, elemental and NMR spectral analyses.

5.2. Representative procedure for the preparation of gem-dibromomethyl compounds

To a solution of methyl-2-chloro-6-methylpyridine-4-carboxylate (27.9 g, 0.151 mol) in CCl_4 (300 mL) was added NBS (53.8 g, 0.302 mol) followed by benzoylperoxide (2.5 g, 0.018 mol). The mixture was gradually heated to reflux for 8 h and cooled to room temperature. The succinimide was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/hexane) to afford 41.8 g (81%) of **1a** as a colourless liquid.

5.2.1. Methyl-2-chloro-6-dibromomethylpyridine-4-carboxylate **1a**

Colourless liquid; R_f (10% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1736, 1554, 1304, 1227, 744, 684 cm^{-1}. [Found: C, 27.91; H, 1.72; N, 4.01. $C_8H_6Br_2ClNO_2$ requires C, 27.98; H, 1.76; N, 4.08%.] δ_H (400 MHz, DMSO-d_6) 8.07 (1H, s, Ph), 7.88 (1H, s, Ph), 7.46 (1H, s, C*H*Br$_2$), 3.91 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 163.6, 159.8, 151.4, 142.2, 125.0, 118.8, 53.7, 41.1.

5.2.2. Methyl-6-dibromomethylpyridine-3-carboxylate **1b**[15]

Following the representative protocol for bromination, 12.7 g of **1b** was isolated by column chromatography as colourless liquid affording 75% yield; ν_{max} (liquid film) 1733, 1436, 1114, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.12 (1H, s, Ph), 8.40–8.37 (1H, dd, *J* 8.2, 2.0 Hz, Ph), 7.89–7.87 (1H, d, *J* 8.2 Hz, Ph), 6.68 (1H, s, C*H*Br$_2$), 3.97 (3H, s, COO*Me*); δ_C (100.6 MHz, $CDCl_3$) 164.7, 162.3, 149.7, 138.8, 126.2, 121.5, 52.6, 40.4.

5.2.3. Ethyl-6-dibromomethylpyridine-2-carboxylate **1c**

Following the general protocol for bromination, 150 g of **1c** was isolated by column chromatography as colourless liquid affording 71% yield; R_f (10% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1737, 1310, 1227, 1139, 662 cm^{-1}. [Found: C, 33.65; H, 2.96; N, 4.23. $C_9H_9Br_2NO_2$ requires C, 33.47; H, 2.81; N, 4.34%.] δ_H (400 MHz, $CDCl_3$) 8.14–8.12 (1H, dd, *J* 7.8, 1.0 Hz, Ph), 8.07–8.05 (1H, dd, *J* 7.7, 1.0 Hz, Ph), 7.98–7.95 (1H, m, Ph), 6.77 (1H, s, C*H*Br$_2$), 4.50–4.45 (2H, q, O*CH*$_2$Me), 1.45–1.41 (3H, t, CH$_2$*Me*); δ_C (100.6 MHz, $CDCl_3$) 164.3, 159.8, 146.1, 138.9, 126.2, 125.4, 62.2, 40.6, 14.2.

5.2.4. Methyl-5-dibromomethylthiophene-2-carboxylate **1d**[15]

Following the general protocol for bromination, 194 g of **1d** was isolated by crystallization from acetonitrile as brown needles affording 82% yield; mp 68–69.5 °C; ν_{max} (KBr) 1713, 1531, 1265, 1094, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64–7.63 (1H, d, *J* 4.0 Hz, Ph), 7.24–7.23 (1H, dd, *J* 4.0, 0.4 Hz, Ph), 6.86 (1H, s, C*H*Br$_2$), 3.89 (3H, s, COO*Me*); δ_C (100.6 MHz, $CDCl_3$) 162.1, 151.9, 134.8, 132.6, 127.1, 52.4, 31.1.

5.2.5. Methyl-5-dibromomethylisoxazole-3-carboxylate **1e**

Following the general protocol for bromination, 57 g of **1e** was isolated by column chromatography as white solid affording 73% yield; mp 59–60 °C; R_f (10% EtOAc/hexane) 0.55; ν_{max} (KBr) 1741, 1471, 1413, 1234, 1014, 718, 624 cm^{-1}. [Found: C, 24.20; H, 1.72; N, 4.60. $C_6H_5Br_2NO_3$ requires C, 24.11; H, 1.69; N, 4.69%.] δ_H (400 MHz, DMSO-d_6) 7.55 (1H, s, Ph), 7.05 (1H, s, C*H*Br$_2$), 3.89 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 170.6, 159.5, 156.7, 103.3, 53.5, 25.0.

5.2.6. Methyl-5-bromo-2-dibromomethylfuran-3-carboxylate **1f**[15]

Following the general protocol for bromination, 368 g of **1f** was isolated by column chromatography as white solid affording 72% yield; mp 147–149 °C; ν_{max} (KBr) 1712, 1498, 1435, 1290, 1064, 699 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.43 (1H, s, Ph), 6.99 (1H, s, C*H*Br$_2$), 3.81 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 160.9, 155.7, 125.4, 114.5, 112.8, 52.5, 25.2.

5.2.7. Methyl-3-dibromomethylthiophene-2-carboxylate **1g**

Following the representative protocol for bromination, 61 g of **1g** was isolated by crystallization from acetonitrile as light brown solid affording 76% yield; mp 44.5–47.5 °C; R_f (10% EtOAc/hexane) 0.65; ν_{max} (KBr) 1705, 1437, 1277, 1080, 693 cm^{-1}. [Found: C, 26.82; H, 1.97. $C_7H_6Br_2O_2S$ requires C, 26.78; H, 1.93%.] δ_H (400 MHz, DMSO-d_6) 7.98–7.96 (1H, d, *J* 5.2 Hz, Ph), 7.68 (1H, s, C*H*Br$_2$), 7.63–7.62 (1H, d, *J* 5.2 Hz, Ph), 3.85 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 161.3, 147.1, 133.4, 130.5, 124.6, 52.7, 32.3.

5.2.8. Ethyl-4-dibromomethylbenzoate **1h**[15]

Following the representative protocol for bromination, 12 g of **1h** was isolated by column chromatography as white solid affording 82% yield; mp 97–99 °C; ν_{max} (KBr) 1704, 1287, 1133, 704, 641 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.07–8.04

(2H, d, *J* 8.4 Hz, Ph), 7.65–7.63 (2H, d, *J* 8.4 Hz, Ph), 6.66 (1H, s, C*H*Br_2), 4.42–4.37 (2H, q, O*CH*$_2$Me), 1.42–1.39 (3H, t, CH_2*Me*); δ_C (100.6 MHz, DMSO-d_6) 165.5, 145.9, 131.6, 129.9, 126.5, 61.2, 39.7, 14.3.

5.2.9. Methyl-4-dibromomethyl-1-naphthoate **1i**

Following the representative protocol for bromination, 18 g of **1i** was isolated by column chromatography as white solid affording 86% yield; mp 90–91 °C; R_f (10% EtOAc/hexane) 0.60; ν_{max} (KBr) 1718, 1515, 1257, 1130, 772, 670 cm^{-1}. [Found: C, 43.68; H, 2.90. $C_{13}H_{10}Br_2O_2$ requires C, 43.61; H, 2.82%.] δ_H (400 MHz, DMSO-d_6) 8.73–8.71 (1H, d, *J* 8.2 Hz, Ph), 8.50 (1H, br s, Ph), 8.29–8.10 (3H, m, Ph), 7.80–7.71 (2H, m, Ph, C*H*Br_2), 3.95 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 167.3, 128.9, 128.5, 127.1, 126.4, 53.0, 40.9.

5.2.10. 6-(Dibromomethyl)-2,2-dimethyl-4H-1,3-benzodioxin-4-one **1j**

Following the representative protocol for bromination, 11 g of **1j** was isolated by crystallization from Et_2O as white solid affording 78% yield; mp 109–110 °C; R_f (10% EtOAc/hexane) 0.75; ν_{max} (KBr) 1726, 1432, 1303, 1153, 1047, 695 cm^{-1}. [Found: C, 37.82; H, 2.97. $C_{11}H_{10}Br_2O_3$ requires C, 37.75; H, 2.88%.] δ_H (400 MHz, DMSO-d_6) 8.08–8.07 (1H, d, *J* 2.3 Hz, Ph), 7.97–7.95 (1H, dd, *J* 8.6, 2.4 Hz, Ph), 7.48 (1H, s, C*H*Br_2), 7.22–7.20 (1H, d, *J* 8.6 Hz, Ph), 1.69 (6H, s, Me_2C); δ_C (100.6 MHz, DMSO-d_6) 159.9, 156.4, 137.4, 136.1, 127.0, 118.8, 112.7, 107.4, 41.2, 25.7.

5.2.11. 7-(Dibromomethyl)-2,2-dimethyl-4H-1,3-benzodioxin-4-one **1k**

Following the general representative protocol for bromination, 9 g of **1k** was isolated by column chromatography as white solid affording 76% yield; mp 84.5–86.6 °C; R_f (10% EtOAc/hexane) 0.75; ν_{max} (KBr) 1729, 1615, 1435, 1305, 1151, 1047, 703 cm^{-1}. [Found: C, 37.72; H, 2.92. $C_{11}H_{10}Br_2O_3$ requires C, 37.75; H, 2.88%.] δ_H (400 MHz, DMSO-d_6) 7.95–7.93 (1H, d, *J* 8.1 Hz, Ph), 7.46–7.44 (1H, dd, *J* 8.1, 1.7 Hz, Ph), 7.39 (1H, s, C*H*Br_2), 7.29–7.28 (1H, d, *J* 1.8 Hz, Ph), 1.68 (6H, s, Me_2C); δ_C (100.6 MHz, DMSO-d_6) 159.7, 155.5, 150.5, 130.6, 121.8, 115.3, 114.1, 107.3, 40.9, 25.7.

5.2.12. Methyl-3-dibromomethyl-4-nitrobenzoate **1l**[15]

Following the representative protocol for bromination, 32 g of **1l** was isolated by column chromatography as yellow solid affording 75% yield; mp 121–123 °C; ν_{max} (KBr) 1727, 1528, 1303, 1109, 863, 645 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.63 (1H, s, Ph), 8.14–8.07 (2H, m, Ph), 7.48 (1H, s, C*H*Br_2), 3.94 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 164.4, 147.5, 135.8, 134.8, 132.6, 125.6, 53.5, 35.8.

5.2.13. Methyl-3-bromo-4-dibromomethylbenzoate **1m**

Following the general protocol for bromination, 16 g of **1m** was isolated as colourless liquid affording 70% yield; R_f (10% EtOAc/hexane) 0.65; ν_{max} (liquid film) 1727, 1556, 1436, 1387, 1114, 723, 625 cm^{-1}. [Found: C, 27.98; H, 1.89. $C_9H_7Br_3O_2$ requires C, 27.94; H, 1.82%.] δ_H (400 MHz, DMSO-d_6) 8.09–8.06 (2H, m, Ph), 8.03–8.00 (1H, m, Ph), 7.32 (1H, s, C*H*Br_2), 3.86 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 164.5, 144.4, 133.7, 132.6, 131.5, 129.7, 120.1, 53.1, 40.6.

5.2.14. 4-Dibromomethyl benzeneboronicacid neopentyl ester **1n**

Following the representative protocol for bromination, 13 g of **1n** was isolated as white solid affording 87% yield; mp 135–137 °C; R_f (10% EtOAc/hexane) 0.75; ν_{max} (KBr) 1475, 1442, 1318, 1135, 651 cm^{-1}. [Found: C, 39.95; H, 4.25. $C_{12}H_{15}BBr_2O_2$ requires C, 39.83; H, 4.18%.] δ_H (400 MHz, DMSO-d_6) 7.73–7.71 (2H, d, *J* 8.2 Hz, Ph), 7.59–7.57 (2H, d, *J* 8.2 Hz, Ph), 7.39 (1H, s, C*H*Br_2), 3.75 (4H, s, O*CH*$_2$), 0.94 (6H, s, Me_2C); δ_C (100.6 MHz, DMSO-d_6) 144.7, 140.8, 134.3, 128.9, 126.1, 71.8, 43.4, 31.9, 21.7.

5.2.15. 5-Dibromomethylbenzo[b]thiophene-2-boronicacid pinacol ester **1o**

Following the representative protocol for bromination, 7.2 g of **1o** was isolated as white solid affording 81% yield; mp 178–179.9 °C; R_f (10% EtOAc/hexane) 0.70; ν_{max} (KBr) 1521, 1431, 1318, 1137, 663 cm^{-1}. [Found: C, 41.76; H, 3.93. $C_{15}H_{17}BBr_2O_2S$ requires C, 41.71; H, 3.97%.] δ_H (400 MHz, DMSO-d_6) 8.15 (1H, s, Ph), 8.10–8.07 (1H, d, *J* 8.4 Hz, Ph), 7.96 (1H, s, Ph), 7.70–7.68 (1H, dd, *J* 8.4, 1.5 Hz, Ph), 7.54 (1H, s, C*H*Br_2), 1.31 (12H, s, CMe_2–CMe_2); δ_C (100.6 MHz, DMSO-d_6) 144.1, 139.9, 139.2, 135.2, 125.0, 123.7, 122.2, 85.0, 43.5, 25.0.

5.2.16. 3-Dibromomethyl-4-fluorobenzeneboronicacid pinacol ester **1p**

Following the representative protocol for bromination, 6.7 g of **1p** was isolated as semisolid affording 82% yield; R_f (10% EtOAc/hexane) 0.65; ν_{max} (KBr) 1607, 1360, 1144, 1102, 852, 629 cm^{-1}. [Found: C, 39.69; H, 4.13. $C_{13}H_{16}BBr_2FO_2$ requires C, 39.64; H, 4.09%.] δ_H (400 MHz, DMSO-d_6) 8.00–7.98 (1H, dd, *J* 8.2, 1.5 Hz, Ph), 7.72 (1H, m, Ph), 7.48 (1H, s, C*H*Br_2), 7.31–7.26 (1H, m, Ph), 1.28 (12H, s, CMe_2–CMe_2); δ_C (100 MHz, DMSO-d_6) 161.9, 159.4, 138.8, 135.4, 129.1, 116.6, 116.4, 84.5, 34.8, 25.1.

5.3. Representative procedure for the hydrolysis of gem-dibromomethylarenes into aldehydes

In a typical procedure, a mixture of methyl-2-chloro-6-dibromomethylpyridine-4-carboxylate **1a** (7 g, 0.0203 mol) and anhydrous pyridine (15.6 mL, 0.203 mol) was refluxed at 100 °C for a given period of time (Entry 1, Table 1). Once the substrate was completely consumed as monitored by TLC, the brown reaction mixture was cooled and poured into ice-cold water (100 mL). The product was extracted with diethyl ether (2×50 mL), the combined organic phase was washed with water and brine solution and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the brown residue was passed through a small plug of silica gel using petroleum ether/ethyl acetate (9/1) to afford 2.92 g (73%) of **2a** as a white solid.

5.3.1. Methyl-2-chloro-6-formylpyridine-4-carboxylate ***2a***

Following the general protocol for hydrolysis, 78 g of **1a** provided 31.7 g of **2a** as white solid affording 70% yield; mp 68–69.8 °C; R_f (10% EtOAc/hexane) 0.40; ν_{max} (KBr) 1736, 1712, 1310, 1217, 761, 683 cm^{-1}. [Found: C, 48.10; H, 3.06; N, 6.96. $C_8H_6ClNO_3$ requires C, 48.14; H, 3.03; N, 7.02%.] δ_H ($CDCl_3$, 400 MHz) 10.06 (1H, s, C*H*O), 8.40 (1H, s, Ph), 8.13 (1H, s, Ph), 4.02 (3H, s, COO*Me*); δ_C (100.6 MHz, $CDCl_3$) 190.8, 163.4, 153.6, 152.9, 141.5, 128.3, 119.4, 53.3.

5.3.2. Methyl-6-formylpyridine-3-carboxylate ***2b***[19]

Following the general protocol for hydrolysis, 8.5 g of **2b** was isolated as white solid affording 72% yield; mp 115–116.7 °C; δ_H (400 MHz, DMSO-d_6) 10.16 (1H, s, C*H*O), 9.38–9.37 (1H, d, *J* 1.2 Hz, Ph), 8.50–8.47 (1H, dd, *J* 8.0, 1.2 Hz, Ph), 8.06–8.03 (1H, dd, *J* 8.0, 0.5 Hz, Ph), 4.01 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 192.5, 164.8, 154.9, 151.1, 138.3, 129.2, 121.1, 52.8.

5.3.3. Ethyl-6-formylpyridine-2-carboxylate ***2c***

Following the general protocol for hydrolysis, 27 g of **2c** was isolated by column chromatography as white solid affording 77% yield; mp 37.5–39.6 °C; R_f (10% EtOAc/hexane) 0.30; ν_{max} (KBr) 1735, 1709, 1292, 1216, 1165 cm^{-1}. [Found: C, 60.41; H, 5.11; N, 7.78. $C_9H_9NO_3$ requires C, 60.33; H, 5.06; N, 7.82%.] δ_H (400 MHz, DMSO-d_6) 10.01 (1H, s, C*H*O), 8.32–8.30 (1H, dd, *J* 7.7, 1.2 Hz, Ph), 8.30–8.21 (1H, m, Ph), 8.14–8.11 (1H, dd, *J* 7.6, 1.2 Hz), 4.42–4.37 (2H, q, O*CH*$_2$Me), 1.36–1.33 (3H, t, CH$_2$*Me*); δ_C (100.6 MHz, DMSO-d_6) 193.0, 164.0, 152.3, 148.2, 139.4, 128.9, 124.6, 61.6, 14.1.

5.3.4. Methyl-5-formylthiophene-2-carboxylate ***2d***[20]

Following the general protocol for hydrolysis, 190 g of **1d** afforded 78 g of **2d** as yellow solid in 76% yield; mp 81–82 °C; δ_H (400 MHz, DMSO-d_6) 9.98 (1H, s, C*H*O), 7.85–7.84 (1H, d, *J* 3.9 Hz, Ph), 7.75–7.74 (1H, d, *J* 3.9 Hz, Ph), 3.95 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 183.3, 161.9, 147.7, 140.9, 135.0, 133.3, 52.8.

5.3.5. Methyl-5-formylisoxazole-3-carboxylate ***2e***[21]

Following the general protocol for hydrolysis, 19 g of **2e** was isolated as white solid affording 72% yield; mp 72–73 °C; δ_H (400 MHz, DMSO-d_6) 10.04 (1H, s, C*H*O), 7.37 (1H, s, Ph), 4.04 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 177.5, 168.9, 159.1, 156.7, 108.8, 53.3.

5.3.6. Methyl-2-bromo-5-formylfuran-4-carboxylate ***2f***

Following the general protocol for hydrolysis, 197.8 g of **2f** was isolated as white solid affording 87% yield; mp 58.3–58.7 °C; R_f (10% EtOAc/hexane) 0.45; ν_{max} (KBr) 1721, 1676, 1473, 1245, 1066 cm^{-1}. [Found: C, 36.17; H, 2.21. $C_7H_5BrO_4$ requires C, 36.08; H, 2.16%.] δ_H (400 MHz, DMSO-d_6) 9.89 (1H, s, C*H*O), 7.22 (1H, s, Ph), 3.86 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 177.5, 160.7, 153.3, 130.6, 127.6, 114.6, 52.8.

5.3.7. Methyl-3-formylthiophene-2-carboxylate ***2g***[22]

Following the general protocol for hydrolysis, 34 g of **2g** was isolated as light brown solid affording 91% yield; mp 52.5–54.4 °C; δ_H (400 MHz, DMSO-d_6) 10.46 (1H, s, C*H*O), 7.94–7.93 (1H, dd, *J* 5.1, 0.7 Hz, Ph), 7.53–7.51 (1H, dd, *J* 5.2, 0.5 Hz, Ph), 3.89 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 186.5, 161.1, 143.8, 138.2, 132.7, 127.0, 52.9.

5.3.8. Methyl-4-formylbenzoate ***2h***[23]

Following the general protocol for hydrolysis, 7.3 g of **2h** was isolated as colourless liquid affording 81% yield; δ_H (400 MHz, DMSO-d_6) 10.1 (1H, s, C*H*O), 8.13–8.11 (2H, d, *J* 8.2 Hz, Ph), 8.03–8.00 (2H, dd, *J* 8.4, 1.2 Hz, Ph), 4.34–4.32 (2H, q, *CH*$_2$Me), 1.34–1.31 (3H, t, CH$_2$*Me*); δ_C (100.6 MHz, DMSO-d_6) 193.3, 165.4, 139.5, 135.0, 130.2, 130.0, 61.7, 14.5.

5.3.9. Methyl-4-formyl-1-naphthoate ***2i***[24]

Following the general protocol for hydrolysis, 10 g of **2i** was isolated as white solid affording 90% yield; mp 95.8–97.5 °C; δ_H (400 MHz, DMSO-d_6) 10.50 (1H, s, C*H*O), 9.19–9.17 (1H, d, *J* 8.4 Hz, Ph), 8.63–8.61 (1H, d, *J* 8.2 Hz, Ph), 8.25–8.19 (2H, m, Ph), 7.82–7.73 (2H, m, Ph), 3.98 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 194.5, 167.4, 134.5, 133.8, 133.8, 130.7, 130.7, 129.5, 128.6, 128.3, 126.1, 124.8, 53.2.

5.3.10. 2,2-Dimethyl-4-oxo-4H-1,3-benzodioxine-6-carbaldehyde ***2j***

Following the general protocol for hydrolysis, 7 g of **2j** was isolated as white solid affording 79% yield; mp 113–114 °C; R_f (10% EtOAc/hexane) 0.55; ν_{max} (KBr) 1740, 1687, 1614, 1268, 1197 cm^{-1}. [Found: C, 64.21; H, 4.95. $C_{11}H_{10}O_4$ requires C, 64.08; H, 4.89%.] δ_H (400 MHz, DMSO-d_6) 9.98 (1H, s, C*H*O), 8.42 (1H, s, Ph), 8.17–8.15 (1H, dd, *J* 8.5, 1.8 Hz, Ph), 7.32–7.30 (1H, d, *J* 8.5 Hz, Ph), 1.73 (6H, s, C*Me*$_2$); δ_C (100.6 MHz, DMSO-d_6) 191.2, 159.6, 159.4, 136.5, 132.1, 131.3, 118.5, 113.1, 107.3, 25.3.

5.3.11. 2,2-Dimethyl-4-oxo-4H-1,3-benzodioxine-7-carbaldehyde ***2k***

Following the general protocol for hydrolysis, 11 g of **2k** was isolated as white solid affording 87% yield; mp 109–111 °C; R_f (10% EtOAc/hexane) 0.55; ν_{max} (KBr) 1738, 1701, 1444, 1389, 1298 cm^{-1}. [Found: C, 64.16; H, 4.87. $C_{11}H_{10}O_4$ requires C, 64.08; H, 4.89%.] δ_H (400 MHz, DMSO-d_6) 10.05 (1H, s, C*H*O), 8.08–8.06 (1H, d, *J* 7.8 Hz, Ph), 7.70–7.68 (1H, dd, *J* 7.9, 1.4 Hz, Ph), 7.60 (1H, s, Ph), 1.72 (6H, s, C*Me*$_2$); δ_C (100.6 MHz, DMSO-d_6) 192.7, 160.0, 156.2, 142.6, 130.7, 123.1, 118.6, 117.7, 107.4, 25.6.

5.3.12. Methyl-3-formyl-4-nitrobenzoate ***2l***[25]

Following the general protocol for hydrolysis, 14 g of **2l** was isolated as white solid affording 90% yield; mp 71.5–73 °C; δ_H (400 MHz, DMSO-d_6) 10.23 (1H, s, C*H*O), 8.39–8.38 (1H, d, *J* 1.5 Hz, Ph), 8.38–8.35 (1H, dd, *J* 8.2, 1.9 Hz,

Ph), 8.25–8.23 (1H, d, *J* 8.2 Hz, Ph), 3.93 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 189.5, 164.5, 151.7, 135.0, 134.4, 131.0, 130.7, 125.5, 53.4.

5.3.13. Methyl-3-bromo-4-formylbenzoate **2m**[26]

Following the general protocol for hydrolysis, 5.6 g of **2m** was isolated as white solid affording 89% yield; mp 76.8–77.6 °C; R_f (10% EtOAc/hexane) 0.55; δ_H (400 MHz, DMSO-d_6) 10.25 (1H, s, C*H*O), 8.22–8.21 (1H, d, *J* 1.5 Hz, Ph), 8.08–8.06 (1H, m, Ph), 7.96–7.94 (1H, d, *J* 8.0 Hz, Ph), 3.89 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 191.3, 164.3, 136.2, 135.4, 134.2, 130.4, 128.7, 125.3, 52.9.

5.3.14. 4-Formylbenzeneboronicacid neopentyl ester **2n**

Following the general protocol for hydrolysis, 8.4 g of **2n** was isolated as white solid affording 93% yield; mp 58–60 °C; R_f (10% EtOAc/hexane) 0.60; ν_{max} (KBr) 2958, 1702, 1481, 1314, 1129 cm^{-1}. [Found: C, 66.18; H, 6.98. $C_{12}H_{15}BO_3$ requires C, 66.10; H, 6.93%.] δ_H (400 MHz, DMSO-d_6) 10.02 (1H, s, C*H*O), 7.89–7.85 (4H, m, Ph), 3.77 (4H, s, OCH_2), 0.93 (6H, s, CMe_2); δ_C (100.6 MHz, DMSO-d_6) 193.9, 138.1, 134.4, 128.9, 71.9, 31.9, 21.7.

5.3.15. 5-Formylbenzo[b]thiophene-2-boronicacid pinacol ester **2o**

Following the general protocol for hydrolysis, 3.6 g of **2o** was isolated as white solid affording 89% yield; mp 102.5–103.7 °C; R_f (10% EtOAc/hexane) 0.55; ν_{max} (KBr) 2977, 1701, 1552, 1349, 1325, 1141 cm^{-1}. [Found: C, 62.48; H, 5.98. $C_{15}H_{17}BO_3S$ requires C, 62.52; H, 5.95%.] δ_H (400 MHz, DMSO-d_6) 10.09 (1H, s, C*H*O), 8.52 (1H, s, Ph), 8.23–8.20 (1H, d, *J* 11.2 Hz, Ph), 8.09 (1H, s, Ph), 7.90–7.86 (1H, dd, *J* 11.2, 2.0 Hz), 1.32 (12H, s, CMe_2–CMe_2); δ_C (100.6 MHz, DMSO-d_6) 193.7, 149.2, 141.1, 136.4, 134.2, 129.0, 125.2, 124.4, 85.6, 25.5.

5.3.16. 3-Formyl-4-fluorobenzeneboronicacid pinacol ester **2p**

Following the general protocol for hydrolysis, 3.5 g of **2p** was isolated as white solid affording 83% yield; mp 51–53.7 °C; R_f (10% EtOAc/hexane) 0.60; ν_{max} (KBr) 2982, 1692, 1605, 1361, 1144, 1109, 851, 662 cm^{-1}. [Found: C, 62.49; H, 6.48. $C_{13}H_{16}BFO_3$ requires C, 62.44; H, 6.45%.] δ_H (400 MHz, DMSO-d_6) 10.21 (1H, s, C*H*O), 8.12–8.11 (1H, d, Ph), 7.98–7.95 (1H, m, Ph), 7.42–7.37 (1H, m, Ph), 1.29 (12H, s, CMe_2–CMe_2); δ_C (100.6 MHz, DMSO-d_6) 188.5, 188.5, 166.8, 164.2, 142.9, 142.8, 136.6, 136.6, 123.9, 123.8, 117.1, 116.9, 84.7, 25.0.

5.4. Representative procedure for the synthesis of 1-deuterio aldehydes from gem-dibromomethylarenes

In a typical procedure, a mixture of **1m** (2 g, 0.005 mol) and anhydrous pyridine (4 mL, 0.05 mol) was heated to 100 °C for 60 min. The brown reaction mixture was then poured into D_2O (10 mL). The product was extracted with diethyl ether (2×15 mL). The combined organic phase was washed with water and brine, and dried. The solvent was removed under vacuum and the residue was passed through a small plug of silica eluting with petroleum ether/ethyl acetate (9/1) to afford 1 g (86%) of the corresponding 1-deuterio aldehyde as a white solid. (However, this compound was contaminated with 8% of **2m** as seen by ^1H NMR analysis.) R_f (10% EtOAc/hexane) 0.55; δ_H (400 MHz, DMSO-d_6) 8.21 (1H, d, *J* 1.2 Hz), 8.08–8.05 (1H, dd, *J* 8.0, 1.4 Hz), 7.96–7.94 (1H, d, *J* 8.0 Hz), 3.89 (3H, s, COO*Me*); δ_C (100.6 MHz, DMSO-d_6) 191.0, 190.8, 190.5, 164.8, 136.0, 134.9, 134.9, 129.7, 128.7, 126.5, 52.8.

Acknowledgements

The authors gratefully acknowledge Dr. Goutam Das, COO, Syngene International Ltd, for his invaluable support.

Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra for all the compounds described in Tables 1–3 are available as Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.030.

References and notes

1. Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; John Wiley and Sons: New York, NY, 1999; p 1224.
2. (a) Chung, S. J.; Kim, D. H. *Tetrahedron* **1995**, *51*, 12549–12562; (b) Segesser; Calvin. *J. Am. Chem. Soc.* **1942**, *64*, 825–826; (c) Sander, W.; Exner, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2285–2290.
3. (a) Tabushi, I.; Sasaki, T. *Tetrahedron Lett.* **1982**, *23*, 1913–1916; (b) Dann, O.; Char, H.; Griessmeier, H. *Liebigs Ann. Chem.* **1982**, *10*, 1836–1869.
4. (a) Li, W.; Li, J.; DeVincentis, D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, *45*, 1071–1074; (b) Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033–6036; (c) Eliel; Rivard. *J. Org. Chem.* **1952**, *17*, 1252–1256; (d) Coleman, G. H.; Honeywell, G. E. *Organic Synthesis Collective*; John Wiley and Sons: New York, NY, 1943; Vol. II, pp 89–91.
5. Bankston, D. *Synthesis* **2004**, *2*, 282–289.
6. (a) Gillespie, J. S.; Acharya, S. P.; Shamblee, D. A.; Davis, R. E. *Tetrahedron* **1975**, *31*, 3–8; (b) Semmelhack, M. F.; Ho, S.; Cohen, G.; Streigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7108–7122.
7. (a) Zondervan, C.; vanden Beuken, E.; Kooijman, H.; Spek, A. L.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 3111–3114; (b) Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227–6238.
8. Waehaelae, K.; Ojanperae, I.; Haeyri, L.; Hase, T. A. *Synth. Commun.* **1987**, *17*, 137–146.
9. Man, Y.-M.; Thomas, C. W.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3214–3221.
10. Jung, M. E.; Hogan, K. T. *Tetrahedron Lett.* **1988**, *29*, 6199–6202.
11. Kröhnke, F.; Leister, H. *Chem. Ber.* **1958**, *91*, 1295.
12. Olofson, R. A.; Zimmerman, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 5057–5059.
13. We also found a spot corresponding to aldehyde due to the decomposition of the bis-pyridinium cation on TLC plate.
14. We have failed in isolating the bis-pyridinium cation due to its spontaneous decomposition to aldehyde. However, in an affirmative study, a mixture of **1m** (1 equiv) and pyridine (10 equiv) was refluxed for 60 min. The crude mixture was then treated with D_2O (5 vol) to afford the

corresponding deuterio aldehyde in 86% yield with a small contamination of **2m**, thus suggesting the formation of bis-pyridinium cation as described by Olofson.[12] The spectral data of the product is provided in Section 5.4.

15. For (**1b**): Tyeklar, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689; (**1d**): Choong, I. C.; Lew, W.; Lee, D.; Pham, P.; Burdett, M. T.; Lam, J. W.; Wiesmann, C.; Luong, T. N.; Fahr, B.; DeLano, W. L.; McDowell, R. S. *J. Med. Chem.* **2002**, *45*, 5005–5022; (**1f**): Khatuya, H. *Tetrahedron Lett.* **2001**, *42*, 2643–2644; (**1h**): See Ref. 23; (**1l**): Aujard, I.; Chouaha, B.; Marine, G.; Odile, R.; Jean-Bernard, B.; Pierre, N.; Ludovic, J. *Chem.—Eur. J.* **2006**, *12*, 6865–6879; (**1n**): Derdau, V.; Oekonomopulos, R.; Gerrit, S. *J. Org. Chem.* **2003**, *68*, 5168–5173.
16. Deshpande, M. S.; Wei, J.; Luo, G.; Cianci, C.; Danetz, S.; Torri, Al.; Tiley, L.; Krystal, M.; Yu, K.-L.; Huang, S.; Gao, Q.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2393–2396.
17. This compound was synthesized following a protocol reported in Ref. 16.
18. Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033–6036.
19. Kozhevnikov, D. N.; Olga, V. S.; Kopchuk, D. S.; Slepukhin, P. A.; Kozhevnikov, V. N. *Tetrahedron Lett.* **2006**, *47*, 7025–7029.
20. Goddard, C. J. *J. Heterocycl. Chem.* **1991**, *28*, 17–28.
21. Simoni, D.; Paolo, I. F.; Rondanin, R.; Stefania, G.; Cannizzo, G.; Barbusca, E.; Porretto, F.; D'Alessandro, N.; Tolomeo, M. *J. Med. Chem.* **1999**, *42*, 4961–4969.
22. Taylor, E. C.; Jennings, L. D.; Zhenmin, M.; Hu, B.; Jun, J.-G.; Zhou, P. *J. Org. Chem.* **1997**, *62*, 5392–5403.
23. Xi, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286–9288.
24. Madsen, P.; Anthony, L.; Michael, P.; Sams, C. K.; Knudsen, L. B.; Sidelmann, U. G.; Ynddal, L.; Brand, C. L.; Andersen, B.; Murphy, D.; Teng, M.; Larry, T.; Dan, K.; John, M.; Atsuo, K.; Shenghua, S.; Michael, D. J.; Kimberly, A. T.; Jun, F.; James, L.; Kenna, A.; Vlad, G.; Jesper, L. *J. Med. Chem.* **2002**, *45*, 5755–5775.
25. Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219–222.
26. Hazlet, S. E.; Bosmajian, G., Jr.; Estes, J. H.; Tallyn, E. F. *J. Org. Chem.* **1964**, *29*, 2034–2036.