Tetrahedron 67 (2011) 3363–3368

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A pattern recognition approach to 14-*epi*-hydrophenanthrene core of the morphine alkaloids based on shikimic acid

Tung N. Dinh [a], Anqi Chen [a,*], Christina L.L. Chai [a,b,*]

[a] Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), n8 Biomedical Grove, Neuros #07-01, Singapore 138665
[b] Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543

ARTICLE INFO

Article history:
Received 15 January 2011
Received in revised form 1 March 2011
Accepted 21 March 2011
Available online 26 March 2011

Keywords:
Pattern recognition
Hydrophenanthrene
Shikimic acid
Intramolecular Heck coupling
Intramolecular McMurry coupling

ABSTRACT

An expeditious and stereoselective construction of C-14-epimer of the tetracyclic hydrophenanthrene framework of the morphine alkaloids is described. The core structure is obtained in nine steps in 11% overall yield from shikimic acid via three key transformations: (i) coupling of shikimic acid with 2-iodoisovanillin at C-3 by double S_N2 inversion to form the aryl ether 5; (ii) an intramolecular Heck reaction to construct the dihydrobenzofuran ring and (iii) a McMurry coupling to furnish the hydrophenanthrene core.

1. Introduction

Pattern recognition is a concept coined by Danishefsky for synthesis planning, especially in natural product synthesis.[1] This concept, which complements that of retrosynthetic analysis pioneered by Corey,[2] emphasizes the importance in the recognition of the connection between a synthetic target and the substructure(s) that is/are easily accessible.

Morphine alkaloids, represented by morphine (**1a**) and codeine (**1b**) (Fig. 1), have long been used as potent analgesics. From a synthetic point of view, these complex natural products, which contain a heavily functionalized pentacyclic skeleton, have stimulated extensive synthetic efforts with a plethora of synthetic studies and total syntheses being reported.[3] Among them, construction of the hydrophenanthrene framework followed by mounting the ethanamine bridge onto this core structure between C-9 and C-13 (morphine numbering) has proven to be a successful strategy.[3f,aa–ff]

(−)-Shikimic acid (**2**), a natural product isolated from star anise fruits, has been used as a versatile chiral building block for the synthesis of many targets including therapeutic drugs[4a–d] such as oseltamivir (Tamiflu).[4b] During our recent work on the synthesis of Tamiflu,[5] we recognized that shikimic acid resembles the lower half of the morphine alkaloid skeleton and could therefore be used as a building block for the synthesis of these alkaloids. On the one hand, the stereogenic centre at C-3 (shikimic acid numbering) is not only to be incorporated into C-5 (morphine numbering) of the morphine system but could also serve to control the installation of the rest of the stereogenic centres in the molecule. The hydroxyl groups at C-4 and C-5 of shikimic acid would provide the latent allylic alcohol motif of the alkaloids via a three-step sequence, i.e., epoxide formation[6] followed by phenylselenide opening-selenoxide elimination.[3jj] On the other hand, the α,β-unsaturated moiety of **2** should enable the installation of the top half of the alkaloids via an intramolecular Heck coupling reaction with 2-iodoisovanillin (**3**). These insights promoted us to embark on the development of a synthetic strategy that would allow us to expeditiously build the hydrophenanthrene framework **7** of the alkaloids as well as gain

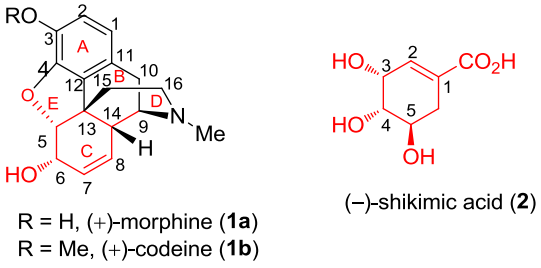


Fig. 1. Structures of shikimic acid, morphine and codeine with the portion in red to be derived from **2**.

* Corresponding authors. E-mail addresses: chen_anqi@ices.a-star.edu.sg (A. Chen), christina_chai@ices.a-star.edu.sg (C.L.L. Chai).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.063

access to a series of simplified morphine analogues for biological evaluation as potential analgesics.

2. Results and discussion

Our strategy (Fig. 2) was to first couple the protected shikimic acid (**4**) at C-3 with 2-iodoisovanillin (**3**) to form the aryl ether **5** via a double S_N2 inversion sequence. The aryl ether **5** would then be cyclized by an intramolecular Heck reaction to provide the dihydrobenzofuran **6** with desired stereochemistry at C-13 as governed by the known C-5 (morphine numbering) configuration inherited from shikimic acid. The fourth ring of the hydrophenanthrene core would be formed either by a ring closing olefin metathesis (RCM) reaction or a McMurry coupling whilst the configuration of C-14 would depend on the stereochemical outcome of the saturation of the double bond in **6**, leading to either the morphine core structure **7a** (R=β-H) or its C-14-epimer **7b** (R=α-H).

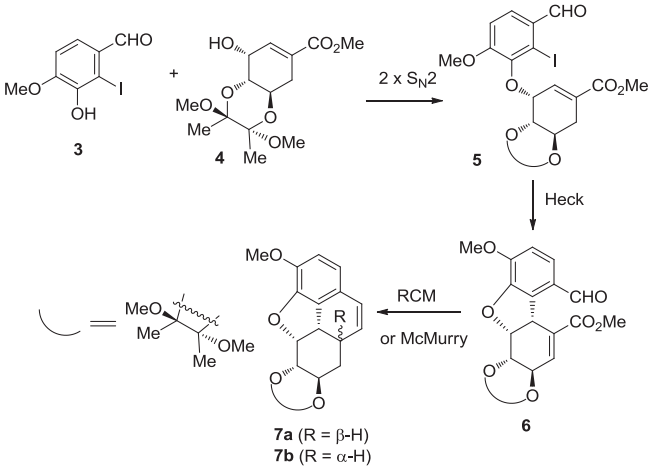
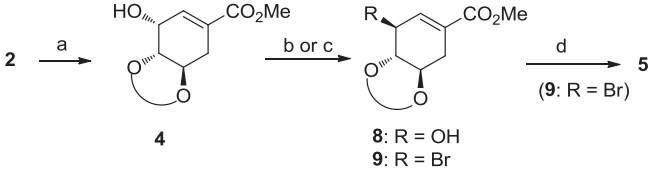


Fig. 2. Forward synthetic analysis of **7**.

In order to couple at the C-3 position of shikimic acid with 2-iodoisovanillin (**3**),[7] it is necessary to protect C-4 and C-5 hydroxyl groups as well as the carboxylic acid. This was achieved selectively in an efficient one-pot protocol[8] by heating **2** with 2,2,3,3-tetramethoxybutane (TMB) formed in situ from 2,3-butanedione and trimethyl orthoformate in methanol in the presence of CSA (Scheme 1).[9] Our initial plan was to couple **3** and **4** using a double Mitsunobu reaction sequence, i.e., by first inversion of the allylic alcohol of **4** with benzoic acid follow by a second inversion with **3**. Although the first inversion proceeded well to provide the desired epimeric alcohol **8** after methanolysis (77% yield over two steps), the second inversion with **3** was unsuccessful under a range of reaction conditions attempted, returning only the starting materials.



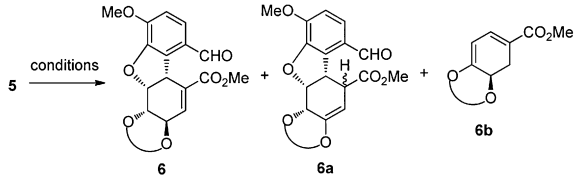
Scheme 1. Synthesis of aryl ether **5**. Reagents and conditions: (a) $(MeCO)_2$, $HC(OMe)_3$, CSA (cat.), MeOH, reflux, 2 days, 70%; (b) (i)-DEAD, Ph_3P, benzoic acid, (ii) K_2CO_3, MeOH, 77% over two steps; (c) (i) MsCl, Et_3N, DCM, 0 °C, 1 h; (ii) LiBr, THF, rt, overnight, 80.5% for **9** over two steps; (d) **3**, K_2CO_3, Ag_2O, DMF, 60 °C, 5 h, 84%.

Given the difficulties encountered in the second Mitsunobu reaction, an alternative double S_N2 inversion sequence, i.e., formation of the more reactive bromide **9** followed by substitution with **3** was investigated. Thus, **4** was converted to its mesylate, which was reacted with lithium bromide to provide a separable mixture of bromide **9** and its C-3 epimer in a ratio of 17:1 in 85% combined yield.

Reaction of **9** with **3** in the presence of potassium carbonate in DMF at room temperature for 18 h, led to an inseparable mixture of aryl ether **5** and its C-3 epimer in a ratio of 8.5:1 in 73% yield. The formation of the epimeric product was rationalized by the epimerization of bromide **9** caused by reversible bromide anion displacement. Based on this rationale, we envisaged that an additive that could capture the bromide anion formed in the reaction would inhibit the formation of the undesired epimer. Indeed, when the reaction was carried out at room temperature in the presence of silver(I) oxide (1 equiv), the formation of the epimer was completely suppressed and the desired aryl ether **5** was obtained as the sole product. The reaction time was significantly shortened to 5 h by heating the reaction at 60 °C, providing **5** in 84% yield.

With the aryl ether (**5**) in hand, we next examined the intramolecular Heck reaction (Table 1).

Table 1
Heck reaction of aryl ether **5**



Entry	Catalyst system[a,b]	Yield[c] (%)			
		5	**6**	**6a**	**6b**
1	$Pd_2(dba)_3$, P(*o*-Tol)$_3$	0	50	24	26
2	$Pd_2(dba)_3$	57	37	3	2
3	$Pd(OAc)_2$, Bu_4NI	67	27	0	5
4	$Pd(OAc)_2$, PPh_3	0	63	6	22
5	$Pd(OAc)_2$, dppe	0	39	<1	60
6	$Pd(OAc)_2$, PCy_3	0	43	0	56
7	$Pd(PPh_3)_4$	0	100 (71[d])	0	0

[a] Reactions were carried out with 0.1 M of **5** in toluene in a sealed tube at 90 °C for 18 h with a catalyst (20 mol %) and a ligand (20 mol %) as indicated.
[b] Triethylamine (2 equiv) was used as the base except for entry 7 where K_2CO_3 (2 equiv) was used.
[c] Yields were based on ^1H NMR spectroscopic analysis of the crude.
[d] Isolated yield.

Initial reaction using $Pd_2(dba)_3$[10] resulted in the formation of a mixture of the desired dihydrobenzofuran **6**, its isomeric product **6a** and diene **6b** (entry 1), which apparently resulted from the elimination of the aryloxy moiety as has been reported previously.[3jj] In view of the poor yields of the desired product and complex product profile, a number of catalyst systems and conditions were screened. While $Pd(OAc)_2$ in combination with different phosphine ligands (entries 4–6) did not improve the formation of the elimination product **6b**, 'ligandless'[11a] (entry 2) and Jeffery-type[11b] (entry 3) conditions gave rather poor conversion although the amount of **6b** formed in the reaction was decreased. Gratifyingly it was found that reaction carried out using $Pd(PPh_3)_4$ as the catalyst, potassium carbonate as the base in toluene at 80 °C,[11c] afforded cleanly the desired product **6** in 71% isolated yield without formation of **6b** (entry 7). The stereochemistry of **6** was confirmed by single crystal X-ray diffraction analysis,[12] revealing a *syn* relationship between C-13 and C-5 as anticipated (Fig. 3).

This also confirmed that the two methoxy groups of the ketal protecting group adopt the *anti* orientation due to the stabilizing effects of the anomeric interactions within the ketal motif.[13]

With the Heck product **6** in hand, we set out to reduce the double bond of the α,β-unsaturated ester. When **6** was hydrogenated under an atmosphere of hydrogen (1 atm) with 10% Pd/C as

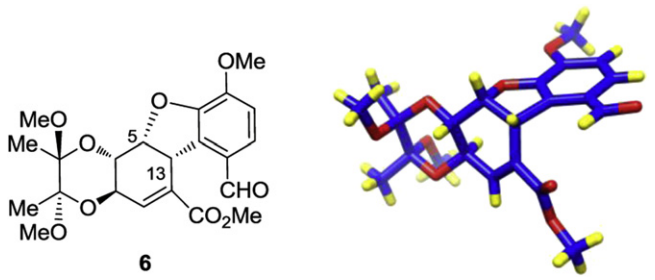
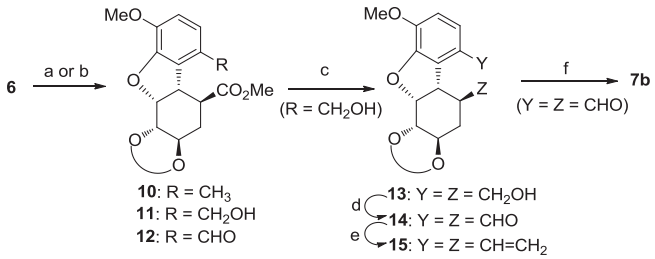


Fig. 3. CHIMERA® representation of the X-ray structure of **6**.

the catalyst, the over-reduced product **10** was obtained instead of the desired aldehyde **12** (Scheme 2). This unexpected product is likely to have formed by the hydrogenation of the aldehyde group to the corresponding benzyl alcohol **11**, which underwent further hydrogenolysis.



Scheme 2. Completion of the synthesis of **7b**. Reagents and conditions: (a) 10% Pd/C, H_2 (1 atm), quant. for (**10**); (b) 10% Pd/C, NH_3 (7 M solution in MeOH, 6 equiv), H_2 (1 atm), quant. for (**11**); (c) DIBAL (4 equiv), THF, 0 °C to rt, quant.; (d) Dess–Martin periodinane, *t*-BuOH, DCM, rt, 2 h, 63%; (e) $Ph_3P^+CH_3,Br^-$ (3 equiv), LiHMDS (3 equiv), THF, 0 °C to rt, 42%; (f) Zn, $TiCl_4$, Py, THF, −10 °C then reflux overnight, 53%.

It is reported that hydrogenolysis of benzylic ethers can be inhibited by additives such as ammonia, pyridine or ammonium acetate.[14] Screening these additives found that addition of ammonia (6 equiv) gave the best result with the compound **11** being obtained in quantitative yield as a single stereoisomer. The configuration of the newly formed stereogenic centre in **11** was assigned by NOE experiments, which revealed that the hydrogen at C-14 is *anti* to that at C-13 (Fig. 4), which is epimeric in relation to that in morphine alkaloids.

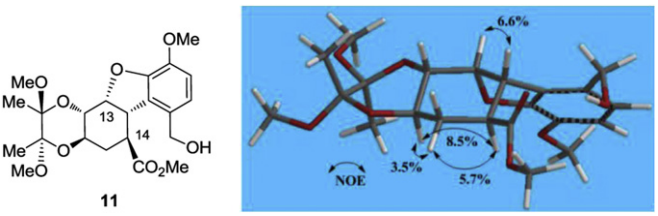


Fig. 4. Energy minimized conformation[15] and NOE's of **11**.

The formation of the fourth ring was explored on **11** with RCM as the first option. In this regard, it was necessary to convert both the hydroxyl and the ester groups of **11** into terminal alkenes required for the RCM reaction. Using an excess of DIBAL, **11** was reduced to the diol **13**, which was further oxidized to the dialdehyde **14** (63% yield) with Dess–Martin reagent in the presence of *t*-BuOH to accelerate the reaction.[16] The dialdehyde was then treated with an excess of Wittig reagent generated from methyltriphenylphosphonium bromide, providing the diene **15** in an unoptimized 42% yield. Unfortunately, despite screening several commercially available ruthenium-based RCM catalysts under various conditions,[17] **15** failed to cyclize and only the starting material was recovered.

To this end, the McMurry coupling[18] approach was explored taking advantage of the dialdehyde **14** that had been obtained for the synthesis of the diene **15**. Gratifyingly, treatment of **14** with a low-valent titanium species generated in situ from titanium(IV) chloride and zinc dust as a reducing agent yielded the hydrophenanthrene **7b** in 53% yield.

3. Conclusions

In summary, we have successfully developed a nine-step, stereoselective route to the 14-*epi*-hydrophenanthrene framework **7** of the morphine alkaloids in 11% overall yield using shikimic acid from the chiral pool as the key building block. The key features of this exploratory route include: coupling of shikimic acid (**2**) with 2-iodoisovanillin (**3**) to form the aryl ether **5** via a double S_N2 inversion, an intramolecular Heck reaction to form the dihydrobenzofuran ring and a McMurry coupling to build the fourth ring of the hydrophenanthrene. This development should enable access to a series of simplified morphine analogues that could have potential analgesic application.

4. Experimental section

4.1. General methods

Melting points were recorded on a capillary melting point apparatus and were uncorrected. Infrared spectra were recorded as KBr discs or evaporated films the data are reported as wavenumber (cm^{-1}). Nuclear magnetic resonance spectra were recorded at 400 MHz for proton and 100 MHz for carbon spectroscopy using $CDCl_3$ as the solvent unless otherwise stated. The chemical shifts (δ) are reported as the shift in parts per million from tetramethylsilane (TMS, 0.00 ppm). High-resolution mass spectra (HRMS) were obtained using electrospray time-of-flight ionization techniques. Microanalyses were performed on a CHNS analyser. Analytical thin layer chromatography (TLC) was conducted on aluminium sheets with silica gel 60 F_{254}. The chromatograms were analyzed under a 254 nm UV lamp and developed using a potassium permanganate 'dipping' solution [$KMnO_4$/potassium carbonate/5% aqueous sodium hydroxide/water (3 g:20 g:5 mL:300 mL)] followed by heating. Flash column chromatography was conducted by using Merck silica gel 60 (40–63 μm) and analytical reagent (AR) grade solvents indicated. All solvents used were of AR grade, purified by literature procedures and where appropriate, stored over freshly activated molecular sieves. All reactions were carried out under an atmosphere of dry, oxygen-free argon unless otherwise specified. Reactions that involved moisture sensitive compounds were carried out using oven-dried apparatus and with anhydrous solvents.

4.2. (2*S*,3*S*,4a*R*,8*R*,8a*S*)-Methyl 2,3-dimethoxy-2,3-dimethyl-8-(methylsulfonyloxy)-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4] dioxine-6-carboxylate (mesylate of 4)

Mesyl chloride (7.12 mL, 91.0 mmol) was added dropwise to a solution of alcohol **4**[8] (21.36 g, 70.6 mmol) and triethylamine (12.9 mL, 92.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The ice bath was then removed and the mixture was stirred at room temperature for 2 h. Saturated NH_4Cl (100 mL) was added. The organic layer was separated and washed with brine (100 mL), dried over $MgSO_4$ then evaporated to dryness under reduced pressure to give the crude mesylate (26.9 g, 100%) as a brown solid pure enough (as judged by ^1H NMR). A sample was purified by column chromatography by gradient elution with ethyl acetate in hexanes (0–20%) to afford the pure *title compound* as a white solid. R_f=0.34 (30% EtOAc/hexane); mp: 127–128 °C; $[\alpha]_D^{21}$ −30 (*c* 1.0, $CHCl_3$); IR (neat) 1707, 1345, 1260, 1173, 1137, 1115, 1043, 918, 890, 872 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 6.82 (dd, J=5.7, 2.5 Hz, 1H), 5.30–5.24 (m, 1H), 4.09 (td, J=10.5, 6.0 Hz, 1H), 3.78–3.74 (m, 1H), 3.76 (s, 3H), 3.28 (s, 3H), 3.25 (s, 3H), 3.15 (s, 3H), 2.88 (ddd, J=18.1, 6.0, 0.8 Hz, 1H), 2.29 (dddd, J=18.1, 10.5, 2.5, 0.8 Hz, 1H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 134.8, 130.9, 100.2, 99.3, 75.3, 69.3, 62.6, 52.5, 48.4, 48.3, 39.2, 30.4, 17.9, 17.7; HRMS (ESI-TOF): 403.1033 ($[M+Na]^+$); $C_{15}H_{24}NaO_9S$ calcd 403.1038.

4.3. (2*S*,3*S*,4a*R*,8*S*,8a*S*)-Methyl 8-bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine-6-carboxylate (9)

LiBr (153 mg, 1.76 mmol) was added portionwise to a solution of the above mesylate (191 mg, 0.50 mmol) in THF (4 mL) at room temperature. The mixture was stirred vigorously overnight before a mixture of dichloromethane (10 mL) and water (10 mL) was added. The organic phase was extracted with dichloromethane (3×10 mL). The combined organic layer was then washed with brine, dried over $MgSO_4$, concentrated to dryness to give yellow oil. Purification by column chromatography (gradient elution with hexane/ethyl acetate (0–10%)) afforded bromide **9** (147 mg, 80.5%), then its 3-epimer (8.3 mg, 4.5%). Data for **9**: R_f=0.51 (20% EtOAc/hexane); mp: 91–92 °C; $[\alpha]_D^{23}$ +214 (*c* 1.3, $CHCl_3$); IR (neat) 1714, 1273, 1185, 1081, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (t, J=2.7 Hz, 1H), 4.66 (dddd, J=8.6, 4.1, 2.7, 1.5 Hz, 1H), 3.93 (dd, J=10.5, 8.6 Hz, 1H), 3.76 (s, 3H), 3.78–3.72 (m, 1H), 3.34 (s, 3H), 3.26 (s, 3H), 2.78 (ddd, J=17.5, 5.5, 1.5 Hz, 1H), 2.38 (dddd, J=17.5, 10.5, 4.1, 2.7 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 137.2, 129.5, 100.0, 99.6, 75.3, 66.6, 52.4, 48.3, 48.3, 47.1, 29.4, 17.8, 17.7; HRMS (ESI-TOF): 387.0414 ($[M+Na]^+$); $C_{14}H_{21}{}^{79}BrNaO_6$ calcd 387.0419 and 389.0408 ($[M+Na]^+$); $C_{14}H_{21}{}^{81}BrNaO_6$ calcd 389.0399. Anal. Calcd for $C_{14}H_{21}BrO_6$: C, 46.04%; H, 5.80%. Found C, 46.17%; H, 5.85%.

4.4. (2*S*,3*S*,4a*R*,8*R*,8a*S*)-Methyl 8-bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine-6-carboxylate (3-*epi* 9)

Data for 3-*epi* **9**: R_f=0.32 (20% EtOAc/hexane); mp: 137–138 °C; $[\alpha]_D^{21}$ −92 (*c* 1.6, $CHCl_3$); IR (neat) 1716, 1441, 1251, 1136, 1117, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, J=5.5, 2.7 Hz, 1H), 4.76–4.74 (m, 1H), 4.19 (td, J=10.5, 6.3 Hz, 1H), 3.76 (s, 3H), 3.62 (dd, J=10.5, 4.4 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 2.93 (dd, J=18.1, 6.3 Hz, 1H), 2.46 (dddd, J=18.1, 10.5, 2.7, 1.3 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 135.4, 129.7, 100.2, 99.3, 68.2, 63.7, 52.4, 48.3, 48.2, 46.6, 30.4, 18.0, 17.8; HRMS (ESI-TOF): 387.0426($[M+Na]^+$); $C_{14}H_{21}{}^{79}BrNaO_6$ calcd 387.0419 and 389.0408 ($[M+Na]^+$); $C_{14}H_{21}{}^{81}BrNaO_6$ calcd 389.0399.

4.5. (2*S*,3*S*,4a*R*,8*R*,8a*S*)-Methyl 8-(3-formyl-2-iodo-6-methoxyphenoxy)-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine-6-carboxylate (5)

In a sealed tube, a suspension of **9** (2.01 g, 5.5 mmol), 2-iodoisovanillin (**3**)[7] (1.53 g, 5.5 mmol), silver(I) oxide (1.27 g, 5.5 mmol) and K_2CO_3 (1.56 g, 11.3 mmol) in DMF (50 mL) was heated at 60 °C for 5 h. The crude reaction mixture was then filtered through a pad of Celite. Water (20 mL) was added to the filtrate, which was extracted with ethyl acetate (5×50 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$ and concentrated to give a yellow oil. Purification by column chromatography on silica gel (hexane/ethyl acetate 4:1) afforded **5** (2.6 g, 84%) as a light yellow foam. R_f=0.66 (50% EtOAc/hexane); mp: 77–78 °C; $[\alpha]_D^{26}$ −76 (*c* 1.0, $CHCl_3$); IR (neat): 1720, 1683, 1575, 1475, 1274, 1131, 1037, 927, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (d, J=0.6 Hz, 1H), 7.65 (d, J=8.6 Hz, 1H), 6.95 (d, J=8.6 Hz, 1H), 6.79 (dd, J=5.4, 2.1 Hz, 1H), 5.36–5.33 (m, 1H), 4.78 (td, J=10.0, 6.3 Hz, 1H), 3.95 (s, 3H), 3.77–3.74 (m, 1H), 3.72 (s, 3H), 3.32 (s, 3H), 3.25 (s, 3H), 3.00 (dd, J=18.3, 6.3 Hz, 1H), 2.36 (ddd, J=18.3, 10.0, 2.1 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 166.6, 156.8, 146.7, 133.4, 133.4, 129.5, 126.4, 112.0, 100.2, 100.2, 99.3, 73.7, 70.6, 63.1, 56.4, 52.4, 48.1, 48.0, 30.8, 18.1, 18.0; HRMS (ESI-TOF): 585.0588 ($[M+Na]^+$); $C_{22}H_{27}INaO_9$ calcd 585.0597.

4.6. (2*S*,3*S*,4a*R*,6a*R*,11a*R*,11b*R*)-Methyl 7-formyl-2,3,10-trimethoxy-2,3-dimethyl-2,3,4a,6a,11a,11b-hexahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6-carboxylate (6)

In a sealed tube containing **5** (2.6 g, 4.63 mmol), $Pd(PPh_3)_4$ (1.08 g, 0.93 mmol) and K_2CO_3 (1.29 g, 9.31 mmol) in toluene (28 mL) was heated at 90 °C for 2 days under argon atmosphere. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1) to yield **6** (1.43 g, 71%) as a brown solid. A further recrystallization (hexane/ethyl acetate) afforded white crystals from which a suitable single crystal was selected for X-ray analysis. R_f=0.57 (50% EtOAc/hexane); mp: 222–223 °C; $[\alpha]_D^{23}$ −12 (*c* 0.9, $CHCl_3$); IR (neat) 1714, 1683, 1603, 1284, 1254, 1142, 1103, 1026, 942 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.45 (d, J=8.5 Hz, 1H), 6.86 (d, J=8.5 Hz, 1H), 6.79–6.77 (m, 1H), 5.10 (dd, J=6.6, 2.4 Hz, 1H), 4.95 (ddd, J=6.6, 2.1, 1.1 Hz, 1H), 4.79 (dt, J=9.5, 1.8 Hz, 1H), 3.98 (dd, J=9.5, 2.4 Hz, 1H), 3.91 (s, 3H), 3.69 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 166.5, 149.5, 148.6, 139.2, 130.2, 130.0, 126.3, 123.4, 112.0, 100.6, 100.2, 81.9, 69.4, 63.3, 56.0, 52.3, 48.1, 48.2, 42.9, 17.8, 17.7; HRMS (ESI-TOF): 435.1657 ($[M+H]^+$); $C_{22}H_{27}O_9$ calcd 435.1655 and 457.1474 ($[M+Na]^+$); $C_{22}H_{26}NaO_9$ calcd 457.1475.

4.7. (2*S*,3*S*,4a*R*,6*S*,6a*S*,11a*R*,11b*S*)-Methyl 7-(hydroxymethyl)-2,3,10-trimethoxy-2,3-dimethyl-2,3,4a,5,6,6a,11a,11b-octahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6-carboxylate (11)

To a solution of **6** (100.7 mg, 0.23 mmol) in EtOH (5 mL) was added 5% Pd/C (50 mg, 10 mol%) and NH_3 (7 M solution in MeOH) (200 μL, 1.4 mmol). The reaction mixture was stirred at room temperature under H_2 (1 atm) for 1 h then filtered through a pad of Celite. The filtrate was concentrated to give **11** as a white solid (101.6 mg, 100%). R_f=0.37 (60% EtOAc/hexane); mp: 213–214 °C; $[\alpha]_D^{29}$ +100.9 (*c* 1.0, $CHCl_3$); IR (neat) 3000, 1709, 1509, 1274, 1131, 1098, 1034, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, J=8.4 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 4.68 (dd, J=5.2, 3.7 Hz, 1H), 4.48 (d, J=12.5 Hz, 1H), 4.34 (d, J=12.5 Hz, 1H), 4.10–4.03 (m, 1H), 3.91 (dd, J=10.3, 3.7 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.68 (dd, J=10.3, 5.2 Hz, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 2.53–2.46 (m, 1H), 2.04 (dt, J=7.9, 4.2 Hz, 1H), 1.96 (br s, 1H), 1.72 (q, J=12.8 Hz, 1H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 147.3, 145.0, 130.8, 129.2, 122.2, 112.3, 100.6, 99.9, 84.9, 70.7, 64.5, 62.6, 55.8, 52.6, 48.1, 48.0, 46.1, 43.3, 32.3, 18.1, 17.8; HRMS (ESI-TOF): 461.1776 ($[M+Na]^+$); $C_{22}H_{30}NaO_9$ calcd 461.1787.

4.8. ((2*S*,3*S*,4a*R*,6*S*,6a*S*,11a*R*,11b*S*)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,4a,5,6,6a,11a,11b-octahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6,7-diyl)dimethanol (13)

To a stirred solution of **11** (350 mg, 0.8 mmol) in THF (20 mL) was added diisobutylaluminium hydride (5.6 mL of 1.0 M solution in toluene, 5.6 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight and then cooled down to 0 °C, quenched by saturated NH_4Cl (20 mL) and extracted with ether (3×10 mL). The combined organic layers was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated

under reduced pressure to give **13** (328 mg, 100%) as a white solid. R_f=0.11 (70% EtOAc/hexane); mp: 240–241 °C; $[\alpha]_D^{21}$ +52 (*c* 1.0, $CHCl_3$); IR (neat) 3100, 1508, 1281, 1117, 1081, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J*=8.4 Hz, 1H), 6.74 (d, *J*=8.4 Hz, 1H), 4.77 (d, *J*=12.9 Hz, 1H), 4.64–4.60 (m, 2H), 4.11 (td, *J*=10.8, 4.1 Hz, 1H), 3.85–3.82 (m, 1H), 3.82 (s, 3H), 3.64 (dd, *J*=11.5, 3.6 Hz), 3.56 (dd, *J*=11.5, 1.9 Hz, 1H), 3.38 (dd, *J*=10.4, 4.7 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 1.77 (dt, *J*=11.5, 3.3 Hz, 1H), 1.66 (q, *J*=12.0 Hz, 1H), 1.58 (t, *J*=11.3 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 144.8, 132.0, 129.0, 121.2, 111.7, 100.6, 99.8, 86.0, 71.4, 66.2, 63.9, 63.7, 55.9, 48.1, 48.0, 42.2, 42.0, 32.3, 18.1, 17.8; HRMS (ESI-TOF): 409.1870 ($[M-H]^-$); $C_{21}H_{29}O_8$ calcd 409.1862.

4.9. (2*S*,3*S*,4a*R*,6*S*,6a*S*,11a*R*,11b*S*)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,4a,5,6,6a,11a,11b-octahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6,7-dicarbaldehyde (14)

To a stirred solution of **13** (678 mg, 1.65 mmol) in dichloromethane (5.5 mL) at room temperature was added sequentially *tert*-butyl alcohol (1.56 mL, 16.4 mmol) and Dess–Martin periodinane (15 mL of 0.3 M solution in dichloromethane, 4.5 mmol). After stirring for 3 h, saturated aqueous sodium hydrogen carbonate (20 mL) and saturated aqueous sodium thiosulfate (20 mL) were added to the mixture, which was extracted with dichloromethane (2×20 mL). The organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column by gradient elution with ethyl acetate in hexane (0–30%) to give **14** (420 mg, 63%) as a white solid. R_f=0.38 (50% EtOAc/hexane); mp: 235–236 °C; $[\alpha]_D^{20}$ −18.2 (*c* 1.06, $CHCl_3$); IR (neat) 1728, 1714, 1683, 1612, 1580, 1434, 1294, 1145, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 9.58 (d, *J*=4.2 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 4.77 (dd, *J*=5.4, 3.7 Hz, 1H), 4.14–4.12 (m, 1H), 4.11–4.09 (m, 1H), 3.96–3.92 (m, 1H), 3.94 (s, 3H), 3.28 (s, 3H), 3.25 (s, 3H), 2.28 (ddt, *J*=13.0, 10.3, 4.2 Hz, 1H), 1.85 (dt, *J*=13.0, 4.2 Hz, 1H), 1.72 (q, *J*=12.1 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 191.4, 150.3, 148.2, 131.2, 129.3, 125.0, 111.3, 100.5, 99.8, 85.3, 70.3, 64.4, 55.9, 53.1, 48.0, 47.9, 41.2, 28.3, 17.7, 17.6; HRMS (ESI-TOF): 407.1701 ($[M+H]^+$); $C_{21}H_{27}O_8$ calcd 407.1700 and 429.1518 ($[M+Na]^+$); $C_{21}H_{26}NaO_8$ calcd 429.1525.

4.10. (2*S*,3*S*,4a*R*,6*R*,6a*S*,11a*R*,11b*S*)-2,3,10-Trimethoxy-2,3-dimethyl-6,7-divinyl-2,3,4a,5,6,6a,11a,11b-octahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran (15)

To a suspension of methyltriphenylphosphonium bromide (257 mg, 0.72 mmol) in THF (10 mL) was added LiHMDS (0.72 mL of a 1.0 M solution in THF, 0.72 mmol) at room temperature. After 30 min, **14** (98 mg, 0.24 mmol) was added quickly in one portion and the reaction mixture was stirred overnight. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the crude product was purified by column chromatography by gradient elution with ethyl acetate in hexane (0–10%) to afford **15** (41.7 mg, 43%) as a white solid. R_f=0.52 (30% EtOAc/hexane); mp: 165–166 °C; ^1H NMR (400 MHz,) δ 7.10 (d, *J*=8.6 Hz, 1H), 6.77 (d, *J*=8.6 Hz, 1H), 6.64 (dd, *J*=17.6, 11.0 Hz, 1H), 5.86–5.78 (m, 1H), 5.57 (dd, *J*=17.6, 1.1 Hz, 1H), 5.11 (dd, *J*=11.0, 1.1 Hz, 1H), 4.97 (d, *J*=10.3 Hz, 1H), 4.89 (dt, *J*=17.1, 1.1 Hz, 1H), 4.65–4.58 (m, 1H), 4.12 (ddd, *J*=11.6, 10.3, 3.7 Hz, 1H), 3.90 (dd, *J*=10.3, 3.7 Hz, 1H), 3.87 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 3.00 (dd, *J*=10.3, 4.8 Hz, 1H), 1.83 (dt, *J*=12.7, 3.7 Hz, 1H), 1.56 (q, *J*=12.7 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 144.9, 139.9, 135.1, 132.1, 126.6, 117.8, 116.1, 112.3, 112.0, 100.6, 99.8, 85.5, 71.4, 65.7, 55.9, 48.1, 48.0, 46.9, 44.4, 34.2, 18.2, 17.9; HRMS (ESI-TOF): 425.1950 ($[M+Na]^+$); $C_{23}H_{30}NaO_6$ calcd 425.1940.

4.11. (5a*R*,1*S*,6a*R*,8*S*,9*S*,10a*S*,10b*R*)-1,8,9-Trimethoxy-8,9-dimethyl-5a,5a1,6,6a,8,9,10a,10b-octahydrofuro[2′,3′,4′,5′:4,5]phenanthro[2,3-*b*][1,4]dioxine (7b)

In a sealed tube containing **14** (40.6 mg, 0.10 mmol) and zinc dust (40 mg, 0.61 mmol) in dry THF (1 mL) was added pyridine (100 μL, 1.24 mmol). The stirred mixture was cooled to −10 °C and titanium(IV) chloride (33 μL, 0.30 mmol) was added dropwise. The mixture was then heated at 80 °C for 20 h before being cooled to room temperature and filtered through a pad of Celite. The filtrate was diluted with ether (5 mL) and washed sequentially with saturated aqueous $NaHCO_3$ solution, brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the crude product by column chromatography by gradient elution with ethyl acetate in hexane (0–30%) afforded **7b** as a colourless film (20 mg, 53%). R_f=0.45 (30% EtOAc/hexane); $[\alpha]_D^{19}$ −91 (*c* 1.0, $CHCl_3$); IR (neat) 1499, 1436, 1262, 1117, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J*=8.0 Hz, 1H), 6.62 (d, *J*=8.0 Hz, 1H), 6.58 (dd, *J*=9.1, 2.9 Hz, 1H), 5.92 (dd, *J*=9.1, 2.7 Hz, 1H), 4.89–4.86 (m, 1H), 4.13 (dd, *J*=10.3, 6.1 Hz, 1H), 3.86 (s, 3H), 3.83 (dd, *J*=10.3, 7.0 Hz, 1H), 3.32 (s, 3H), 3.20 (s, 3H), 2.96 (dd, *J*=14.6, 7.6 Hz, 1H), 1.96–1.87 (m, 1H), 1.82 (dt, *J*=11.8, 3.3 Hz, 1H), 1.56–1.50 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.7, 133.1, 132.2, 128.0, 126.8, 118.2, 112.7, 100.9, 100.0, 81.0, 72.4, 69.4, 56.4, 48.3, 47.9, 44.7, 40.5, 30.8, 18.1, 17.8; HRMS (ESI-TOF): 397.1629 ($[M+Na]^+$); $C_{21}H_{26}NaO_6$ calcd 397.1627.

Acknowledgements

We thank Dr. Aitipamula Srinivasulu (ICES) and Ms. Chia Sze Chen (ICES) for X-ray crystallographic analysis. Financial support for this work was provided by Agency for Science, Technology and Research (A*STAR), Singapore.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.03.063. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2007**, *72*, 4293–4305; (b) Lee, J. H.; Zhang, Y.; Danishfsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 14330–14333.
2. (a) Corey, E. J. *Pure Appl. Chem.* **1967**, 19–37; (b) Corey, E. J.; Wipke, W. T. *Science* **1969**, *166*, 178–192; (c) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455–612; (d) Corey, E. J.; Cheng, X.-M. The Logic of Chemical Synthesis; Wiley-VCH: New York, NY, **1995**.
3. For reviews see: (a) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Stabile, M. *A Historic Perspective of Morphine Synthesis*, In *Studies in Natural Products Chemistry*, Vol. 18; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1996**, pp 43–154; (b) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159–1168; (c) Hudlicky, T.; Zezula, J. *Synlett* **2005**, 388–405; For total and formal syntheses of morphine and morphine-like alkaloids: (d) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109–1110; (e) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393; (f) Elad, D.; Ginsburg, D. *J. Am. Chem. Soc.* **1954**, *76*, 312–313; (g) Grewe, R.; Fischer, H. *Chem. Ber.* **1963**, *96*, 1520–1528; (h) Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550–1558; (i) Barton, D. H. R.; Bhakuni, D. S.; James, R.; Kirby, G. W. *J. Chem. Soc. C* **1967**, 128–132; (j) Morrison, G. C.; Waite, R. O.; Shavel, J., Jr. *Tetrahedron Lett.* **1967**, *8*, 4055–4056; (k) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. C* **1969**, 2030–2033; (l) Schwartz, M. A.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239–1240; (m) Beyerman, H. C.; Lie, T. S.; Maat, M.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 24–25; (n) Lie, T. S.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 419–420; (o) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135–3137; (p) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, 285–288; (q) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227–238; (r) White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron* **1983**, *39*,

2393–2397; (s) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473–475; (t) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694–4708; (u) Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959–5966; (v) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689; (w) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3927–3933; (x) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449–455; (y) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029; (z) Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453–3456; (aa) Mulzer, J.; Duerner, G.; Trauner, D. *Angew. Chem., Int. Ed.* **1996**, *35*, 2830–2832; (bb) Mulzer, J.; Bats, J. W.; List, B.; Opatz, T.; Trauner, D. *Synlett* **1997**, 441–444; (cc) Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908–5918; (dd) Mulzer, J.; Trauner, D. *Chirality* **1999**, *11*, 475–482; (ee) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250–5251; (ff) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871–7884; (gg) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* **2001**, 1094–1095; (hh) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416–12417; (ii) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543; (jj) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803; (kk) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311–5313; (ll) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Heterocycles* **2009**, *77*, 1219–1234; (mm) Omori, A. T.; Finn, K. J.; Leisch, H.; Carroll, R. J.; Hudlicky, T. *Synlett* **2007**, 2859–2862; (nn) Verin, M.; Barré, E.; Iorga, B.; Guillou, C. *Chem.—Eur. J.* **2008**, *14*, 6606–6608; (oo) Tanimoto, H.; Saito, R.; Chida, H. *Tetrahedron Lett.* **2008**, *49*, 358–362; (pp) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. *J. Am. Chem. Soc.* **2009**, *131*, 11402–11406; (qq) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045–16047.

4. (a) Floss, H. G. *Nat. Prod. Rep.* **1997**, 433–452; (b) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044–2051; (c) Schuster, M. C.; Mann, D. A.; Buchholz, T. J.; Johnson, K. M.; Thomas, W. D.; Kiessling, L. L. *Org. Lett.* **2003**, *5*, 1407–1410; (d) Miao, H.; Tallarico, J. A.; Hayakawa, H.; Munger, K.; Duffner, J. L.; Koehler, A. N.; Schreiber, S. L.; Lewis, T. A. *J. Comb. Chem.* **2007**, *9*, 245–253.
5. Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60–63.
6. For the epoxide formation from *trans*-1,2-diols, see McGowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381–2383 and references cited therein.
7. Compound **3** was synthesized according to procedures described in Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992**, *35*, 466–479.
8. Shih, T. L.; Wu, S. H. *Tetrahedron Lett.* **2000**, *41*, 2957–2959.
9. Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897–3899.
10. Conditions adapted from Ref. 3kk.
11. (a) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859–4862; (b) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687–4690; (c) Pilger, C.; Westermann, B.; Flörke, U.; Fels, G. *Synlett* **2000**, 1163–1165.
12. The X-ray structure was produced using the UCSF Chimera package, University of California, San Francisco, USA. The Data have been deposited at Cambridge Crystallographic Data Centre under deposition no. CCDC 797136 at www.ccdc.cam.ac.uk.
13. Ley, S. V.; Priepke, H. W. M.; Warriner, S. L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2290–2292.
14. Sajiki, H. *Tetrahedron Lett.* **1985**, *36*, 3465–3468.
15. The energy minimized conformations were obtained by using the MMFF94 force field, Spartan 04 version for Windows, Wavefunction, Inc.
16. Tojo, G.; Fernandez, M. *Hypervalent iodine compounds*. Oxidation of Alcohols to Aldehydes and Ketones, A Guide to Current Practice; Springer: New York, 2006, Chapter 3.
17. Catalysts used: Grubb (I), Grubb (II), Grubb–Hoveyda (I), Grubb–Hoveyda (II).
18. McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524.