Tetrahedron 66 (2010) 646–652

Contents lists available at ScienceDirect

Tetrahedron

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

Reactions promoted by [hydroxy(tosyloxy)iodo]benzene in pyrazino-[1,2–*b*]isoquinolines

Irene Ortín, Juan Francisco González, Elena de la Cuesta, Carmen Avendaño *

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

ARTICLE INFO

Article history:
Received 14 October 2009
Received in revised form 13 November 2009
Accepted 16 November 2009
Available online 18 November 2009

Keywords:
Quinones
Oxidations
Hypervalent iodine
Heterocycles
Antitumor agents

ABSTRACT

The hypervalent iodine reagent PhI(OH)OTs (HTIB) promoted oxidative demethylation of 1,4-hydroquinone methyl ethers to give quinones in a quantitative conversion. The efficacy of this reaction, that has been applied to simple arene compounds and to heterocyclic systems, such as 2-isopropoxycarbonyl-7,10-dimethoxy-pyrazino[1,2–*b*]isoquinoline-4-ones and 1,4-diones to get the corresponding 7,10-quinones (compounds **6**–**8**), is similar to those promoted by CAN and does not require the presence of water. Instead of oxidative demethylation, HTIB promoted in 1-methoxy-pyrazino[1,2–*b*]isoquinoline-4-ones complex multi-step processes to give compounds **9** or **10**.

1. Introduction

Heterocyclic quinones are common natural products that often have interesting biological properties, with special relevance as antitumor compounds. Among those containing the isoquinolin-equinones,[1] there are rather simple alkaloids, such as mimosamycin,[2] renierone,[3] or mimocin,[4] and more complex structures that contain a pyrazino[1,2–*b*]isoquinoline core, such as saframycins,[5] naphthyridomycin,[6] cyanocycline A,[7] bioxalomycins,[8] cribrostatin IV,[9,10] and lemonomycin[11,12] (Fig. 1).

We have previously shown that pyrazino[1,2–*b*]isoquinoline compounds, such as **1**[13,14] and **2**,[14,15] are synthetic precursors of interesting antitumor derivatives, such as compounds **3**[13,16] and **4**[17–19] (Fig. 2).

In this context, we were interested in the synthesis of quinones derived from compounds **1**–**3** and in the generation of a C(11)–C(11a)–double bond in compounds **1a**–**1c**. The last objective was first assayed in **1b** through a tandem radical bromination/dehydrohalogenation,[15] but the method was found here inappropriate (**5b** was obtained in 15% yield) because of competitive reactions such as benzylic brominations at C-11 and at the benzyloxymethyl chain[20] (Scheme 1).

To get this aim, we then considered the use hypervalent iodine(III) reagents and, especially, of [hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs) (also known as HTIB or Koser's reagent).[21–24] HTIB is moderately electrophilic at iodine, delivering tosylate groups to a range of organic substrates. Its electrophilic attack to the α-position of ketones[25,26] and to the α-carbon glycine templates[27] lead to quite unstable λ^3-iodane derivatives that make possible nucleophilic substitutions or the introduction of an α,β-unsaturation with reductive loss of iodobenzene. In this paper we present the details of our investigations with this reagent.

2. Results and discussion

Expecting an electrophilic attack to the enol form of the C(1)-carbonyl group, we first examined the reaction of **1c**[13] with HTIB (0.5 equiv) in acetonitrile, but we recovered the starting material. By increasing the amount of HTIB up to 1.5 equiv we got compound **5c** in very low yield together with the *p*-quinone derivative **6c** formed by oxidative demethylation of the C-7 and C-10 methoxyl groups. Addition of a large excess of HTIB, up to 4 equiv, afforded exclusively **6c**.[28] We corroborated that compound **5c** it is not a precursor of the quinone because it could not be converted into **6c** by further treatment with HTIB (Scheme 2).

The relative amounts of compounds **1c**, **5c**, and **6c** at different times and HTIB/**1c** ratios were studied in the ^{1}H NMR spectra of the crude products obtained after evaporation of the solvent. In these spectra, the H-6 proton signals at 6.41, 6.01 and 5.69 ppm were chosen as characteristics of compounds **5c**, **1c**, and **6c**, respectively. We observed a decrease in the **1c**/**6c** ratio by increasing the equivalents of HTIB up to 1.5 equiv without affecting the intensity

* Corresponding author. Tel.: +34 913941821; fax: +34 913941822.
E-mail address: avendano@farm.ucm.es (C. Avendaño).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.070

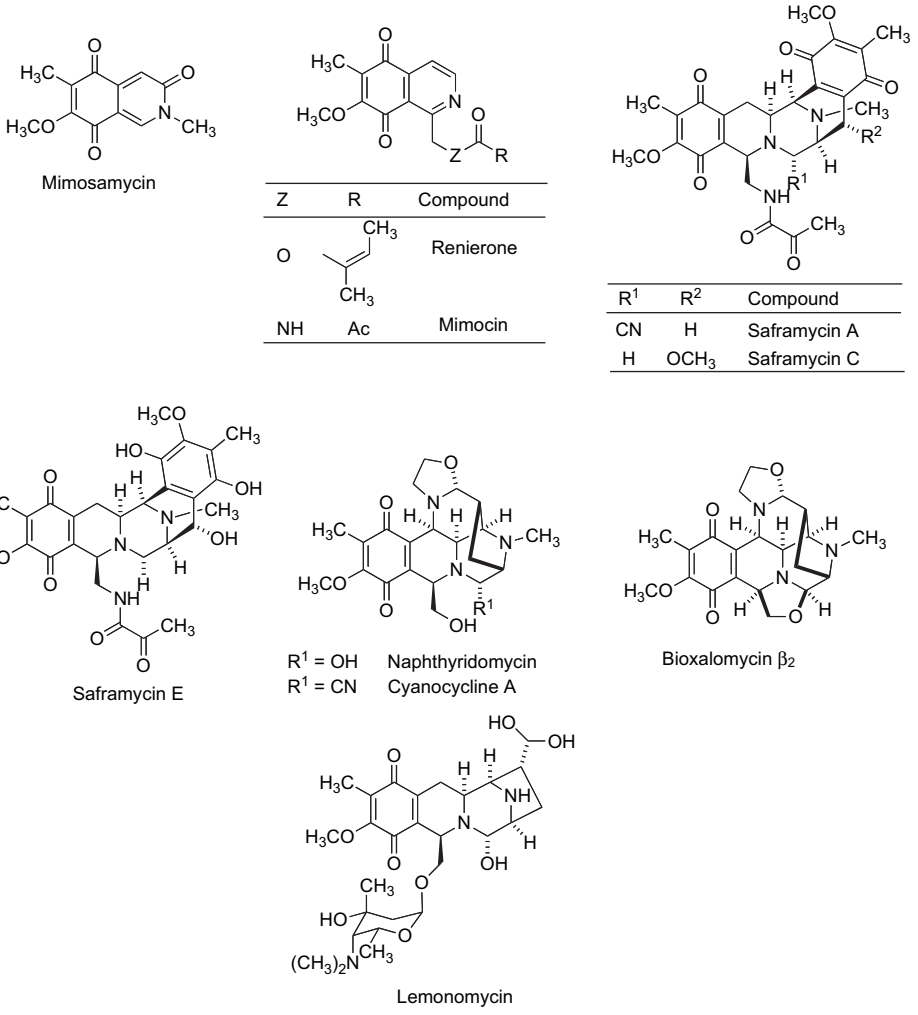


Figure 1.

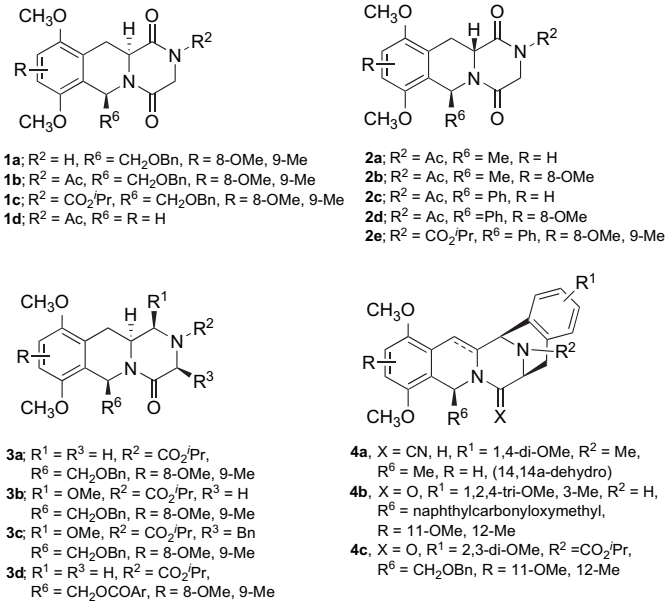
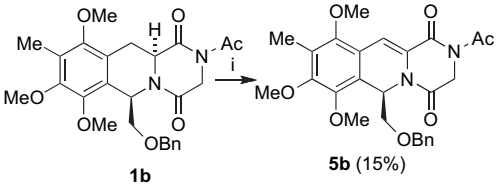


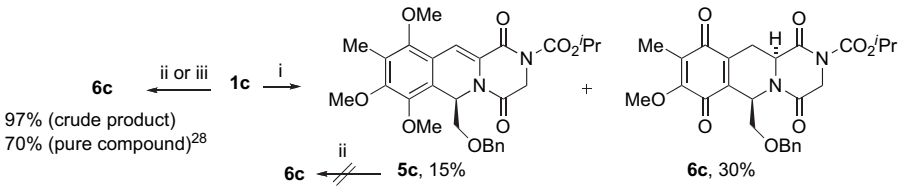
Figure 2.



Scheme 1.

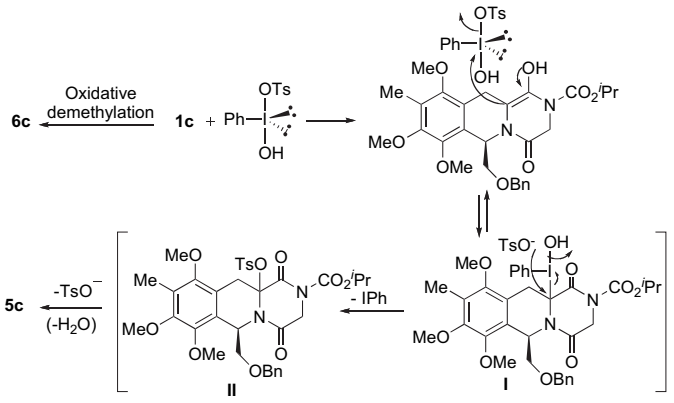
of the signal corresponding to **5c**, and the disappearance of this signal after 10 min of treatment with 2.5 equiv of HTIB, obtaining the same results with dry acetonitrile as solvent. The fact that an excess of HTIB does not give **5c** is difficult to explain. It is possible that λ^3-iodane reverts to the starting material **1c** (Scheme 3).

Oxidative demethylation of hydroquinone methyl ether functional groups is one of the most effective methods to obtain quinones in the later stages of a synthetic scheme. It is usually performed with cerium(IV) ammonium nitrate (CAN),[29–31] nitric acid,[32,33] manganese dioxide(MnO_2)-nitric acid,[34] silver(II) oxide (AgO)-mineral acid,[35] cobalt(III) fluoride (CoF_3),[36] or NBS–H_2SO_4.[37] Although hypervalent iodine(III) reagents[38–52] are particularly attractive organo-oxidants widely used in several oxidative transformations, such as the oxidation of phenols, hydroquinones, and alkoxyphenols to give quinones,[53–58] only BTI [bis(trifluoroacetoxy)iodobenzene] has been used, as far as we know, in the oxidative demethylation of *p*-



i: HTIB (1.5 equiv.), CH_3CN, 90 °C, 2h. ii: HTIB (4 equiv.), CH_3CN, 90 °C, 2h. iii: HTIB (2.5 equiv.), CH_3CN, 90 °C, 10 min.

Scheme 2.



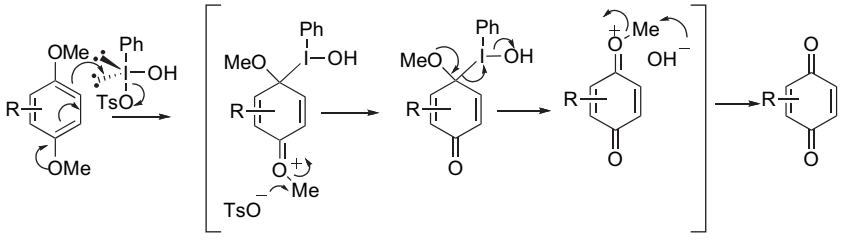
Scheme 3.

dimethoxy arenes.[59,60] According to the plausible mechanism proposed by the authors of this precedent paper, the use of BTI requires water as an external nucleophile.

Considering that the above described HTIB-mediated-oxidative demethylation works in anhydrous conditions, we propose a mechanism that involves a *C*-iodanylated cyclohexadienone (Scheme 4). The bulkiness of the primary adducts explains the found 1,4-regioselectivity.

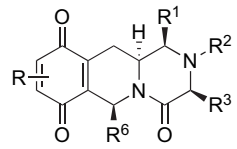
To study the scope of this procedure, the reaction conditions established for **1c** (10 min of treatment with 2.5 equiv of HTIB in refluxing acetonitrile) were applied to compounds **1a**, **1d**, **2a**–**2e**, and **3a**, as well as to simple arene derivatives such as 1,4-dimethoxy and 1,2,4-trimethoxy-benzene. To our pleasure, we obtained *p*-benzoquinone, 2-methoxy-*p*-benzoquinone and the heterocyclic 7,10-quinones **6a**, **6d**, **7a**–**7e**, and **8a** as the only reaction products, although their chromatographic purification implied a significant loss of material[28] and yields between 64–75% for pure heterocyclic quinones (Fig. 3). Besides the characteristic disappearance of the C(7)- and C(10)-methoxy signals and the appearance of the C(7)- and C(10)-carbonyl groups, lower chemical shifts respect to their precursors of the H-6 protons are characteristic in the quinones.

According to the proposed mechanism, methyl tosylate could be isolated by column chromatography from some crude products. We also corroborated that, although we performed the work-up of the reactions by extraction with CH_2Cl_2 followed by water-washing and evaporation, direct evaporation of the reaction mixture is also possible when necessary. Finally, we confirmed that the efficacy of



Scheme 4.

6a; R^2 = H, R^6 = CH_2OBn, R = 8-OMe, 9-Me (71%)
6c; R^2 = $CO_2{}^i$Pr, R^6 = CH_2OBn, R = 8-OMe, 9-Me (70%)
6d; R^2 = Ac, R^6 = R = H (70%)



8a; R^1 = R^3 = H, R^2 = $CO_2{}^i$Pr, R^6 = CH_2OBn, R = 8-OMe, 9-Me (69%)

7a; R^2 = Ac, R^6 = Me, R = H (68%)
7b; R^2 = Ac, R^6 = Me, R = 8-OMe (64%)
7c; R^2 = Ac, R^6 = Ph, R = H (73%)
7d; R^2 = Ac, R^6 =Ph, R = 8-OMe (75%)
7e; R^2 = $CO_2{}^i$Pr, R^6 = Ph, R = 8-OMe, 9-Me (68%)

Figure 3.

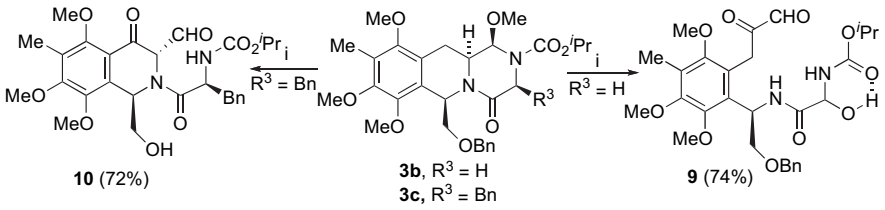
Table1
Comparison between HTIB and CAN

Entry	Starting Compound	Reaction conditions	Yield %	Products
1	**1a**	*A*	71	**6c**
		B	72	
2	**1c**	*A*	70	**6a**
		B	67	
3	**2a**	*A*	68	**7a**
		B	70	

(*A*): HTIB (2.5 equiv), acetonitrile, 90 °C, 2 h.
(*B*): CAN (2.2 equiv), acetonitrile/H_2O (5/2), rt, 30 min.

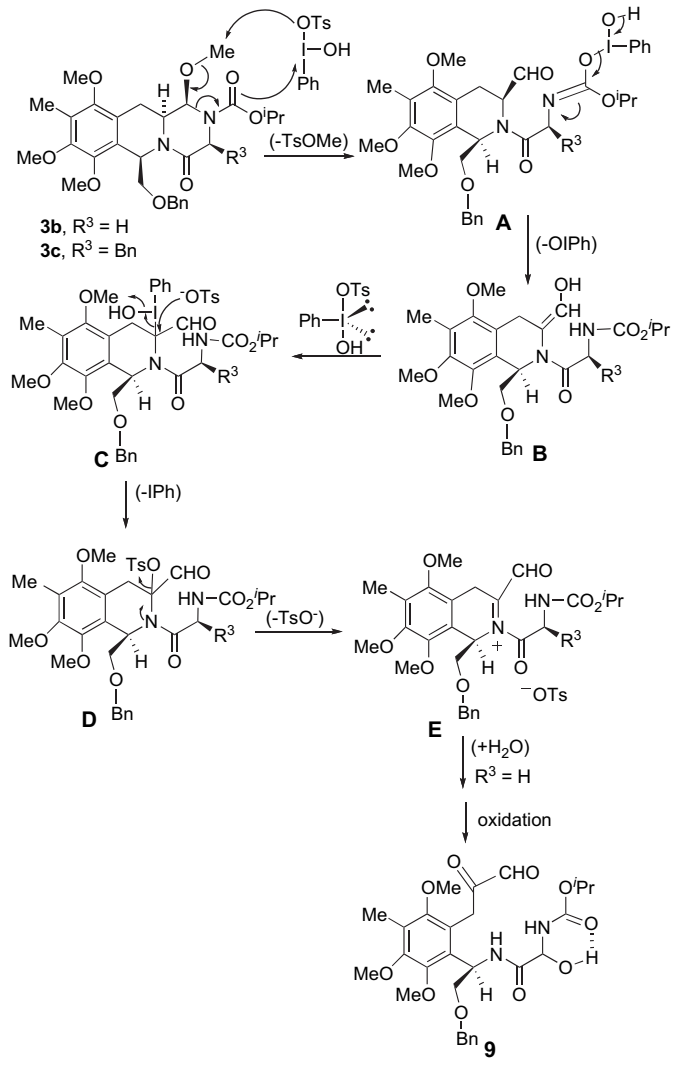
1-Methoxy compounds **3b**[19] (R^3=H) and **3c**[19] (R^3=Bn) gave, instead of the expected *p*-quinones, the benzene and isoquinoline derivatives **9** and **10**, respectively, whose structures were unequivocally established by spectroscopy (Scheme 5).

Spectroscopic data of compound **9** showed the persistence of the benzyloxymethyl chain of **3b** and the presence of four carbonyl signals at δ=171.9, 170.7, 162.5, and 152.9 ppm that were unequivocally assigned to *N*-hydroxyglycinyl, ketone, aldehyde, and carbamate carbonyl groups, respectively. In the ^{1}H NMR spectrum, two doublets at 5.30 and 5.00 ppm were assigned to



Scheme 5.

these HTIB-mediated reactions in compounds **1a**, **1c**, and **2a** (method A, Table 1) is similar to those promoted in the same substrates by the electron transfer oxidizing agent CAN (method B).



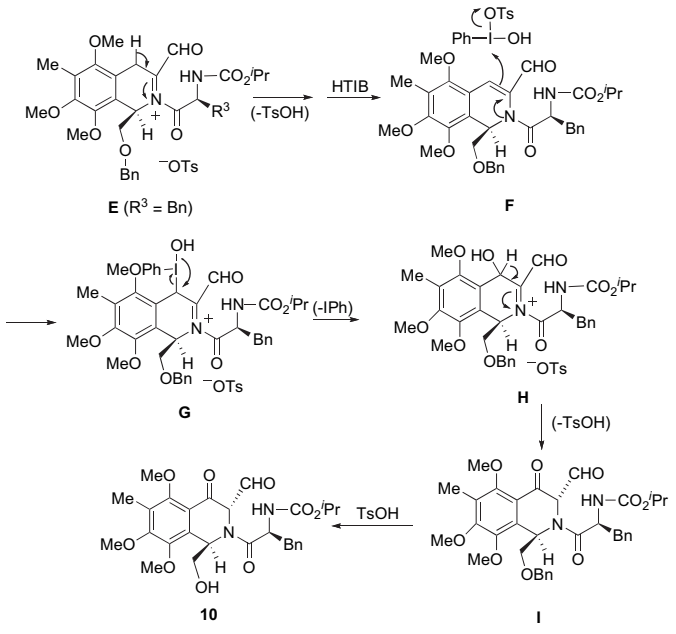
Scheme 6.

CH(OH) and NH protons of the *N*-isopropoxycarbonyl-hydroxyglycine portion, which is probably stabilized by an intramolecular hydrogen bond (the IR spectrum showed the OH absorption at 3391 cm^{-1}). After interchange with D_2O, the NH signal disappeared, while the CH(OH) signal was converted into a singlet at 5.28 ppm.

Spectroscopic data of compound **10** showed the disappearance of the *O*-benzyl group and of the CH_2 signal at C-11 of **3c**, The ^{1}H NMR spectrum showed the presence of two CH–CH_2 systems, a signal at δ=9.15 ppm corresponding to CHO group, and an uncoupled proton at δ=5.37 ppm (H(3)-isoquinoline proton). The NOE observed in one of the CH_2OH protons signal (δ=4.06 ppm) after irradiation of the H(3)-proton, showed that the formyl group is in a *anti*-relationship respect to the chain at C(1) because of a thermodynamic equilibration. Two strong absorption bands at 1737.6 and 1715.5 cm^{-1} in the IR spectrum, and four ^{13}C NMR carbonyl signals at δ=169.5, 168.6, 162.5, and 152.7 ppm are also characteristic. All NMR signals could be assigned by COSY, HMQC, and HMBC experiments (see Experimental and Supplementary data).

We propose that compounds **9** and **10** are formed through a multi-step process that begin with a non-oxidative demethylation of the 1-methoxy hemiaminal group, with elimination of methyl tosylate and iodosylbenzene, to give the isoquinoline-3-carbaldehyde intermediate **B** (enol tautomer). Isolation of methyltosylate in the chromatographic purification of compounds **9** and **10** validates this proposition. Attack of HTIB would give the λ^3-iodane derivative **C** that by reductive loss of iodobenzene would afford the tosylate **D** and, subsequently, the acyliminium cation **E** (the appearance of a transient red color is in favor of this proposal). This species may give **9** after hydrolysis and a second oxidation at the glycine–methylene side chain (Scheme 6).

Alternatively, the acyliminium cation **E** (R^3=Bn) may give the enamine **F** that would form the λ^3-iodane derivative **G** (a tosylate iminium salt) by HTIB attack. After subsequent elimination of iodobenzene to give **H** and of TsOH to give **I**, compound **10** would be formed by *O*-debenzylation of the ether side-chain promoted by TsOH (Scheme 7). Although oxidation of **F** could involve the previously formed iodosylbenzene (PhIO), widely used as an oxygen source[42] with ability to promote the epoxidation of highly electron deficient enones,[61] we think that it is unlikely because of the predictable low reactivity of **E** due to the extended conjugation of the double bond with the phenyl ring system.



Scheme 7.

3. Conclusions

In conclusion, we have developed a practical oxidative protocol that provides a route to *p*-quinones from *p*-dimethoxyarenes and to heterocyclic *p*-quinones from accessible 7,9-dimethoxy-pyrazino[1,2–*b*]isoquinoline-4-ones and 1,4-diones by using the relatively innocuous oxidant HTIB. This procedure is comparable to the use of CAN, is selective for 1,4-dimethoxy compounds without affecting methyl ether functional groups at 1,2-positions and may be performed in anhydrous conditions. We have also discovered a very complex oxidative rearrangement of 1-methoxy derivatives. This work expands the current interest and research activity in the development of synthetic methods based on the organic chemistry of hypervalent iodine reagents.

4. Experimental

4.1. General

The reagents used were of commercial origin (Aldrich, Fluka) and were employed without further purification. Solvents (SDS, Scharlau) were purified and dried by standard procedures. Reactions were monitored by thin-layer chromatography, using Macherey–Nagel or Merck plates with fluorescent indicator. Separations by flash liquid chromatography were performed using silica gel from SDS 60 ACC (230–400 mesh) or Merck (60, 40–63 μm) and aluminum oxide from Merck (90, 70–230 mesh).

Melting points are uncorrected, and were determined using a Hoffler hot stage microscope. Spectroscopic data were obtained with the following instruments: IR, Perkin Elmer Paragon 1000 FTIR; NMR, Bruker AC-250 (250 MHz for ^{1}H and 63 MHz for ^{13}C), Bruker DPX-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or Bruker AV III-700 (700 MHz for ^{1}H and 175 MHz for ^{13}C). (Servicio de Resonancia Magnética Nuclear, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY, NOESY, and ^{13}C–^{1}H HMBC and HMQC correlation experiments. Combustion elemental analyses were obtained by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Perkin Elmer 2400 CHN and a Leco CHNS 932 microanalyzer.

*4.1.1. (**6R***)-6-Benzyloxymethyl-2-N-isopropyloxycarbonyl-7,8,10-trimethoxy-9-methyl-2,3-dihydro-6H-pyrazino[1,2–b]isoquinoline-1,4-dione (**5c**).* [Hydroxy(tosyloxy)iodo]benzene (HTIB) (224 mg, 0.57 mmol) was added to a solution of compound **1c** (200 mg, 0.38 mmol) in acetonitrile (15 mL) and the reaction mixture was stirred for 10 min at 90 °C. The solvent was evaporated and the residue was solved in DCM. The organic solution was washed with H_2O (20 mL×2) and with a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give a residue that was purified by flash column chromatography on silica gel with hexane/ethyl acetate (9:1) as eluant to give **5c** (30 mg, 0.057 mmol) (15% yield) and **6c** (57 mg, 0.114 mmol) (30% yield).

Compound **5c**: Brown solid, mp: 68–69 °C; IR (NaCl) ν_{max}, 1775, 1694; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.35–7.33 (m, 2H), 7.20–7.18 (m, 3H), 6.30 (dd, *J*=8.8 and 3.8 Hz, 1H), 5.07 (sept, *J*=6.3 Hz, 1H), 4.71 (d, *J*=17.3 Hz, 1H), 4.59 (d, *J*=12.1 Hz, 1H), 4.36 (d, *J*=12.1 Hz, 1H), 4.06 (d, *J*=17.3 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.42 (dd, *J*=10.7 and 8.8 Hz, 1H), 3.31 (dd, *J*=10.7 and 3.8 Hz, 1H), 2.11 (s, 3H), 1.27 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.6, 159.2, 153.6, 152.6, 151.2, 145.7, 137.8, 128.3, 127.6, 127.5, 126.1, 125.3, 122.3, 118.9, 114.6, 72.5, 72.4, 69.2, 62.1, 60.7, 60.1, 47.7, 47.5, 21.7, and 9.3. Anal. Calcd for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34. Found: C, 63.92; H, 6.08; N, 5.15.

4.2. General experimental procedure for reactions with HTIB

[Hydroxy(tosyloxy)iodo]benzene (HTIB) (559 mg, 1.43 mmol) was added to a solution of the starting compound (0.57 mmol) in acetonitrile (15 mL) and the reaction mixture was stirred for 10 min at 90 °C. The solvent was evaporated and the residue was solved in DCM. The organic solution was washed with H_2O (20 mL×2) and with a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give a residue that was purified by flash column chromatography.

4.3. Reactions from compounds 1, 2, and 3a

4.3.1. (6R,11aS*)-6-Benzyloxymethyl-8-methoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**6a**).* The residue was purified by flash column chromatography on silica gel with DCM/ethyl acetate (1:1) as eluant to give **6a** (71% yield) as a brown solid, mp: 140–142 °C; IR (NaCl) ν_{max}, 3267, 1668; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 6.79 (s, 1H), 5.74 (s, 1H), 4.78 (dd, *J*=11.2 and 4.0 Hz, 1H), 4.58 (d, *J*=12.1 Hz, 1H), 4.41 (d, *J*=12.1 Hz, 1H), 4.09 (s, 2H), 3.98 (s, 3H), 3.88–3.85 (m, 2H), 3.37 (dd, *J*=18.9 and 4.8 Hz, 1H), 2.52–2.44 (m, 1H), 2.00 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 186.1, 180.7, 166.6, 161.4, 155.6, 140.1, 137.3, 135.8, 128.8, 128.5, 127.9, 127.8, 73.3, 71.0, 60.9, 52.5, 48.6, 44.5, 27.9 and 8.8. Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.22; H, 5.58; N, 6.72.

4.3.2. (6R,11aS*)-6-Benzyloxymethyl-2-N-isopropyloxycarbonyl-8-methoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**6c**).* The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **6c** (70% yield) as a yellow solid, mp: 65–66 °C; IR (NaCl) ν_{max}, 1780, 1728, 1672, 1658 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.20 (m, 5H), 5.60 (bs, 1H), 5.06 (sept, *J*=6.3 Hz, 1H), 4.79 (dd, *J*=11.4 and 4.6 Hz, 1H), 4.46 (d, *J*=12.2 Hz, 1H), 4.39 (d, *J*=18.1 Hz, 1H), 4.30 (d, *J*=12.2 Hz, 1H), 4.17 (d, *J*=18.1 Hz, 1H), 3.88 (s, 3H), 3.80 (dd, *J*=16.5 and 4.0 Hz, 2H), 3.27 (dd, *J*=19.8 and 4.6 Hz, 1H), 2.49 (dd, *J*=19.8 and 11.4 Hz, 1H), 1.90 (s, 3H), 1.31 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 185.7, 180.6, 165.0, 161.7, 155.4, 151.0, 140.1, 137.1, 135.8, 128.8, 128.5, 127.9, 127.8, 73.2, 72.7, 70.8, 60.9, 54.3, 48.6, 47.3, 27.5, 21.6, and 8.7. Anal. Calcd

for $C_{26}H_{28}N_2O_8$: C, 62.89; H, 5.68; N, 5.64. Found: C, 62.82; H, 5.58; N, 5.56.

*4.3.3. N-Acetyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**6d**).* The residue was purified by flash column chromatography on silica gel with DCM/ethyl acetate (9:1) as eluant to give **6d** (70% yield) as an orange solid, mp: 87–88 °C; IR (NaCl) ν_{max}, 1706, 1658; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.75 (s, 2H), 5.22 (d, J=18.7 Hz, 1H), 4.50 (d, J=18.7 Hz, 1H), 4.23 (d, J=18.7 Hz, 1H), 4.19 (dd, J=11.6 and 7.5 Hz, 1H), 3.84 (d, J=18.7 Hz, 1H), 3.32 (dd, J=18.6 and 7.5 Hz, 1H), 2.55 (s, 3H), 2.52 (dd, J=18.6 and 11.6 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 184.7, 184.6, 171.7, 166.3, 162.6, 138.1, 137.7, 136.4, 136.3, 55.7, 45.6, 39.3, 27.3, and 27.1. Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.57; H, 4.32; N, 9.66.

4.3.4. (6S,11aR*)-2-N-Acetyl-6-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**7a**).* The residue was chromatographed with DCM/ethyl acetate (8:2) to give **7a** (68% yield) as an orange solid, mp: 95–97 °C; IR (NaCl) ν_{max}, 1709, 1659; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.73 (s, 2H), 5.67 (dd, J=13.7 and 6.8 Hz, 1H), 4.51 (d, J=18.7 Hz, 1H), 4.31 (dd, J=11.6 and 4.5 Hz, 1H), 4.12 (d, J=18.7 Hz, 1H), 3.22 (dd, J=18.3 and 4.5 Hz, 1H), 2.55 (s, 3H), 2.60–2.50 (m, 1H), 1.39 (d, J=6.8 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 185.1, 184.4, 171.7, 166.6, 161.3, 142.1, 137.9, 136.7, 136.0, 51.9, 45.6, 44.2, 27.5, 27.3, and 18.4. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.72; H, 4.59; N, 9.16.

4.3.5. (6S,11aR*)-2-N-Acetyl-8-methoxy-6-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**7b**).* The residue was purified by flash column chromatography on silica gel with DCM/ethyl acetate (1:1) as the eluant to give **7b** (64% yield) as an orange solid, mp: 93–94 °C; IR (NaCl) ν_{max}, 1707, 1681, 1651, 1609; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.66 (q, J=6.9 Hz, 1H), 4.52 (d, J=18.7 Hz, 1H), 4.33 (dd, J=11.7 and 4.5 Hz, 1H), 4.12 (d, J=18.7 Hz, 1H), 3.78 (s, 3H), 3.26 (dd, J=19.3 and 4.5 Hz, 1H), 2.56 (s, 3H), 2.53 (dd, J=19.3 and 11.7 Hz, 1H), 1.39 (d, J=6.9 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 184.9, 179.4, 171.7, 166.7, 161.3, 158.5, 140.2, 138.6, 107.0, 56.5, 52.0, 45.7, 44.2, 27.8, 27.3, and 18.3. Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.92; H, 4.58; N, 8.66.

4.3.6. (6S,11aR*)-2-N-Acetyl-6-phenyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**7c**).* The residue was chromatographed with hexane/ethyl acetate (3:7) to give **7c** (73% yield) as a yellow solid, mp: 91–92 °C; IR (NaCl) ν_{max}, 2928, 1713, 1660; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 6.94 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 4.53 (d, J=18.7 Hz, 1H), 4.25 (dd, J=11.7 and 4.5 Hz, 1H), 4.12 (d, J=18.7 Hz, 1H), 3.81 (dd, J=19.5 and 4.5 Hz, 1H), 2.65 (dd, J=19.5 and 11.7 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 185.1, 183.7, 171.8, 166.5, 161.2, 139.7, 137.0, 136.7, 136.3, 129.2, 129.0, 128.3, 128.1, 51.7, 50.7, 45.9, 27.8, and 27.4. Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.76; H, 4.58; N, 7.52.

4.3.7. (6S,11aR*)-2-N-Acetyl-8-methoxy-6-phenyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**7d**).* The residue was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give **7d** (75% yield) as an orange solid, mp: 98–99 °C; IR (NaCl) ν_{max}, 2940, 1708, 1682, 1649, 1609; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.84 (s, 1H), 5.95 (s, 1H), 4.53 (d, J=18.7 Hz, 1H), 4.23 (dd, J=11.6 and 4.5 Hz, 1H), 4.12 (d, J=18.7 Hz, 1H), 3.76 (s, 3H), 3.33 (dd, J=19.2 and 4.5 Hz, 1H), 2.64 (dd, J=19.2 and 11.6 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 185.0, 178.8, 171.9, 166.8, 161.5, 158.9, 140.7, 137.9, 137.0, 129.1, 128.9, 128.2, 107.2, 56.5, 51.8, 50.6, 45.7, 27.9, and 27.3. Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10. Found: C, 64.12; H, 4.58; N, 7.06.

4.3.8. (6S,11aR*)-2-N-Isopropyloxycarbonyl-8-methoxy-9-methyl-6-phenyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2–b]isoquinoline-1,4,7,10-tetraone (**7e**).* The residue was chromatographed with hexane/ethyl acetate (7:3) to give **7e** (68% yield) as an orange oil; IR (NaCl) ν_{max}, 1711, 1663; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.21 (m, 5H), 6.78 (s, 1H), 5.12 (sept, J=6.3 Hz, 1H), 4.54 (d, J=16.4 Hz, 1H), 4.36 (d, J=16.4 Hz, 1H), 4.39–4.29 (m, 1H), 3.91 (s, 3H), 3.30 (dd, J=19.8 and 5.9 Hz, 1H), 2.89 (dd, J=19.8 and 11.6 Hz, 1H), 2.00 (s, 3H), 1.36 (d, J=6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.4, 184.9, 164.4, 160.8, 150.9, 141.3, 139.1, 136.9, 136.1, 129.2, 129.1, 128.4, 128.0, 72.9, 57.0, 51.4, 51.1, 47.5, 28.8, 21.6, and 18.3. Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.42; H, 5.39; N, 6.12.

4.3.9. (6R,11aS*)-6-Benzyloxymethyl-2-N-isopropyloxycarbonyl-8-methoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2–b]isoquinoline-4,7,10-trione (**8a**).* The residue was chromatographed with hexane/ethyl acetate (1:1) to give **8a** (69% yield) as an orange oil; IR (NaCl) ν_{max}, 2980, 1698, 1651; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.05 (m, 5H), 5.65 (ws, 1H), 4.88 (sp., J=6.2 Hz, 1H), 4.47 (d, J=12.1 Hz, 1H), 4.32 (d, J=12.1 Hz, 1H), 4.10–4.04 (m, 1H), 3.92–3.86 (m, 1H), 3.88 (s, 3H), 3.86–3.80 (m, 1H), 3.77–3.69 (m, 2H), 3.57–3.49 (m, 2H), 2.68 (dd, J=18.8 and 3.5 Hz, 1H), 2.30 (dd, J=18.8 and 11.3 Hz, 1H), 1.88 (s, 3H), 1.17 (d, J=6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 186.4, 181.1, 164.8, 155.5, 154.5, 141.0, 137.6, 136.5, 128.7, 128.4, 127.8, 127.7, 73.2, 71.5, 69.8, 61.0, 49.1, 48.5, 47.9, 44.1, 27.4, 22.1, and 8.7. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.42; H, 6.58; N, 5.46.

4.4. Reactions from compounds 3b and 3c

*4.4.1. 2-N-[1-Benzyloxymethyl-1-(2,3,5-trimethoxy-4-methyl-6-(2,3-dioxopropyl)-phenylmethyl)]-isopropyloxycarbonyl-1-hydroxy-glycinamide (**9**).* The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **9** (74% yield) as orange oil. (NaCl) ν_{max}, 2936, 1748, 1712, 1697 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.39–7.29 (m, 2H), 7.09–7.05 (m, 3H), 5.96 (t, J=2.1 Hz, 1H), 5.30 (d, J=11.8 Hz, 1H), 5.18 (sept, J=6.2 Hz, 1H), 5.05 (s, 2H), 5.00 (d, J=11.8 Hz, 1H), 4.63 (d, J=12.1 Hz, 1H), 4.39 (d, J=12.1 Hz, 1H), 3.89–3.85 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.74–3.70 (m, 1H), 2.73 (s, 3H), 1.36 (d, J=6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.9, 170.7, 162.5, 153.0, 152.9, 152.3, 144.9, 135.7, 128.5, 128.3, 127.9, 126.8, 124.0, 123.9, 73.6, 72.0, 70.1, 66.4, 62.5, 60.3, 60.0, 53.6, 47.5, 21.8, and 9.5. Anal. Calcd for $C_{28}H_{36}N_2O_{10}$: C, 59.99; H, 6.47; N, 5.00. Found: C, 59.72; H, 6.28; N, 4.86.

4.4.2. (1S)-Hydroxymethyl-2-(2-N-isopropoxycarbonyl-(S*)-phenyl-alanyl)-5,7,8-trimethoxy-6-methyl-4-oxo-1,2,3,4-tetrahydro-isoquinoline-3-carbaldehyde (**10**).* The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **10** (72% yield) as brown oil. (NaCl) ν_{max}, 2940, 1738, 1716 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.40–7.17 (m, 5H), 6.31 (dd, J=2.3 and 0.9 Hz, 1H), 5.54 (dd, J=7.9 and 6.4 Hz, 1H), 5.37 (s, 1H), 5.01 (sept, J=6.3 Hz, 1H), 4.06 (dd, J=8.2 and 2.3 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.76 (s, 3H), 3.52 (dd, J=13.7 and 6.4 Hz, 1H), 3.51 (dd, J=8.2 and 0.9 Hz, 1H), 3.13 (dd, J=13.7 and 7.9 Hz, 1H), 2.20 (s, 3H), 1.28 (d, J=6.3 Hz, 3H), 1.24 (d, J=6.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.0, 168.6, 162.5, 152.8, 152.7, 151.3, 143.9, 137.9, 129.8, 128.2, 128.0, 126.6, 126.3, 123.0, 72.3, 71.3, 66.4, 62.8, 61.7, 60.4, 58.9, 47.8, 35.1, 21.6, 21.5, and 9.4. Anal. Calcd for $C_{28}H_{34}N_2O_9$: C, 61.98; H, 6.32; N, 5.16. Found: C, 61.73; H, 6.18; N, 5.03.

Acknowledgements

This work was supported by CICYT CTQ2006-10930/BQU, and Comunidad Autónoma de Madrid (Group 920234 grant). A FPI fellowship to I. Ortín is also acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.11.070.

References and notes

1. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. Arai, T.; Yazawa, K.; Mikami, Y. *J. Antibiot.* **1976**, *29*, 398–407.
3. McIntyre, D. E.; Faulkner, D. J.; Engen, D. V.; Clardy, J. *Tetrahedron Lett.* **1979**, *20*, 4163–4166.
4. Kubo, A.; Nakamura, S.; Iwata, R.; Takahashi, K.; Arai, T. *Tetrahedron Lett.* **1980**, *21*, 3207–3208.
5. Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015–1018.
6. Sygusch, J.; Brisse, F.; Hanessian, S.; Klupfel, D. *Tetrahedron Lett.* **1974**, *15*, 4021–4023.
7. Hayashi, T.; Noto, T.; Nawata, Y.; Okazaki, H.; Sawada, M.; Ando, K. *J. Antibiot.* **1982**, *35*, 771–777.
8. Bernan, V. S.; Montenegro, D. A.; Korshalla, J. D.; Maiese, V. M.; Steinberg, D. A.; Greenstein, M. *J. Antibiot.* **1994**, *47*, 1417–1424.
9. Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793–798.
10. Saito, N.; Sakai, H.; Suwanborirux, K.; Pummangura, S.; Kubo, A. *Heterocycles* **2001**, *55*, 21–28.
11. Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83–86.
12. He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067–2071.
13. Ortin, I.; González, J. F.; de la Cuesta, E.; Manguan-García, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16*, 9065–9078.
14. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2004**, *60*, 6319–6326.
15. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett.* **2003**, *44*, 4395–4398.
16. Ortin, I.; González, J. F.; de la Cuesta, E.; Manguan-García, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2009**, *17*, 8040–8047.
17. González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2007**, *15*, 112–118.
18. Ortin, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201–2211.
19. Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 9944–9951.
20. Huang, R. L.; Lee, K. H. *J. Chem. Soc.* **1964**, 5957–5962.
21. Koser, G. F.; Relenyi, G. F.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487–2489.
22. Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365–383.
23. Prakash, O.; Saini, N.; Sharma, P. K. *Heterocycles* **1994**, *38*, 409–431.
24. Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89–102.
25. Lee, J. C.; Park, J. Y.; Yoon, S. Y.; Bae, Y. H.; Lee, S. J. *Tetrahedron Lett.* **2004**, *45*, 191–193.
26. Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, Th. *Synlett* **2007**, 538–542.
27. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem.* **2001**, *66*, 5731–5735.
28. Because these quinones are quite instable in solution, a careful column chromatography purification was required to get pure analytical samples.
29. Zhu, X.-Z.; Chen, Ch-F *J. Org. Chem.* **2005**, *70*, 917–924.
30. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.
31. Imamoto, T. *Lanthanide Reagents in Organic Synthesis*; Academic: London, 1994; Chapter 5.
32. Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 499–531.
33. Shaikh, Y. A. *Org. Prep. Proced. Int.* **1976**, *8*, 293–297.
34. Araya, R.; Tapia, R.; Valderrama, J. A. *J. Chem. Res., Synop.* **1987**, 84–85.
35. Scheepers, B. A.; Klein, R.; Davies-Coleman, M. T. *Tetrahedron Lett.* **2006**, *47*, 8243–8246.
36. Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* **1999**, 1474–1476.
37. Kim, D. W.; Choi, H. Y.; Lee, K.-J.; Chi, D. Y. *Org. Lett.* **2001**, *3*, 445–447.
38. Varvoglis, A. *Synthesis* **1984**, 709–726.
39. Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244–250.
40. Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: Weinheim, 1992.
41. Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.
42. Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: London, 1997.
43. Moriarty, R. M.; Prakash, O. *Adv. Heterocycl. Chem.* **1998**, *69*, 1–87.
44. Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273–418.
45. Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287.
46. Togo, H.; Katohki, M. *Synlett* **2001**, 565–581.
47. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584.
48. Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903.
49. Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665.
50. Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, 113–128.
51. Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627–630.
52. Tohma, H.; Kita, Y. J. *Syn. Org. Chem. Jpn.* **2004**, *62*, 116–127.
53. Ficht, S.; Mülbaier, M.; Giannis, A. *Tetrahedron* **2001**, *57*, 4863–4866.
54. Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.
55. Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517–1520.
56. Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126–127.
57. Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829.
58. Lebrasseur, N.; Fan, G.-J.; Oxoby, M.; Looney, M. A.; Quideau, S. *Tetrahedron* **2005**, *61*, 1551–1562.
59. Tohma, H.; Marioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899–6902.
60. Marminon, C.; Gentili, J.; Barret, R.; Nebois, P. *Tetrahedron* **2007**, *63*, 735–739.
61. McQuaid, K. M.; Pettus, T. R. R. *Synlett* **2004**, 2403–2405.