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Synthesis of Indole Substituted Twistenediones from a 2-Quinonyl Boronic Acid

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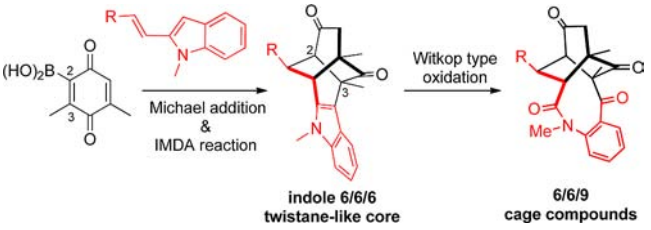
ABSTRACT



Indole substituted twistane-like derivatives resulted in a reaction between 3,5-dimethyl-2-quinonyl boronic acid and 2-alkenyl indoles. Their MCPBA oxidation gave 6/6/9 caged systems. Boronic acid acts as a temporal promoter allowing a site-selective conjugate addition of the heteroaromatic system to the methyl substituted C-3 quinone carbon, giving an intermediate diene which is regioselectively trapped by intramolecular [4 + 2] cycloaddition.

Twistane (tricyclo[4.4.0.0^{3,8}]decane), the twist-boat isomer of adamantane, and its simple functionalized derivatives were first synthesized in 1962.[1] In sharp contrast to adamantane analogues which have received huge attention,[2] these cage-shaped systems have been the subject of limited studies. To date, theoretical investigations[3,4] and applied studies directed toward determining their behavior as liquid crystals[5] have been reported. The D_2 symmetry makes them ideal models to evaluate the chiroptical properties of twist-boat type structures.[6] Some reactivity studies evidenced that the rearrangement of 2-twistanols promoted by acid opens a direct access to adamantane-cage-shaped structures.[1b] Moreover, 4-ketotwistane has shown antiviral activities.[7] Despite these features, only a limited number of syntheses en route to this skeleton are available. These are generally based on intramolecular enolate alkylations of prefunctionalized bicyclo[2.2.2]octan-2-one[1] or *cis*-bicicyclo[4.4.0]-decanediones.[8] More direct strategies based on a two-bond disconnection through an intramolecular Diels–Alder cycloaddition (IMDA) have proven to favor the formation of a less strained 5/6/6 isotwistane (tricyclo[4.3.1.0^{3,7}]decane) framework (Scheme 1).[9]

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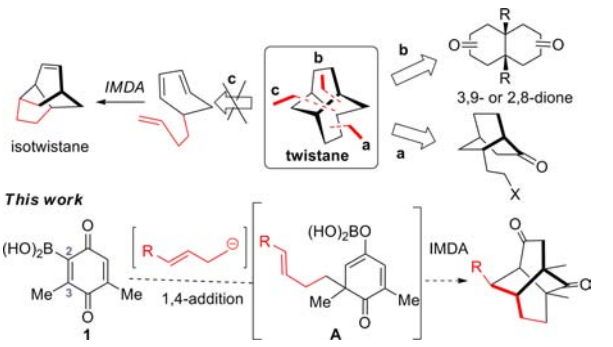
Scheme 1. Synthetic Approaches to the Twistane Framework



Recently, we have synthesized quinonyl boronic acid **1** and achieved highly efficient and regioselective Diels–Alder reactions[10] and Friedel–Crafts (FC)[11] alkylation reactions. The 1,4-addition of indoles to 3-methyl-2-quinonyl boronic acids occurred under very mild conditions, exclusively at the β-substituted C-3 position, and was followed by a protodeboronation. We also demonstrated the formation of an intermediate boron dienolate such as **A** (Scheme 1) that could be trapped *in situ* in an intermolecular [4 + 2] cycloaddition with *N*-phenylmaleimide.[11] Inspired by these results, we reasoned that the boron dienolate intermediate generated from 1,4-addition could be intramolecularly captured in a reaction with an appropriate dienophile. Herein, we report a domino process based on a 1,4-addition/intramolecular Diels–Alder/protodeboronation domino process which occurred when 2-benzoquinonyl boronic acid **1** reacted with 2-alkenylindoles having a substituent at C-2′ in the alkene moiety. This method allows a direct access to densely functionalized twistenedione-like systems, in sharp contrast to the reported IMDA process leading to the isotwistane analogues.[9] A key feature of our approach is the presence of an electron donating group at C-2′ in the alkene dienophile which controlled the regiochemistry of the IMDA.

Quinones are excellent substrates for domino reactions, especially when cycloaddition reactions are involved.[12−14] *p*-Benzoquinones have also been used as Michael acceptors in 1,4-addition reactions, which are accompanied by enolization leading to the corresponding substituted hydroquinone derivatives. 2,3-Dihydrobenzofurans can be obtained by Lewis acid catalyzed 1,4-addition of 1,3-dicarbonyl compounds followed by a sequential enolization and intramolecular cyclization.[15] Similarly, the reaction of β-enaminoesters with benzoquinones can give indoles (Nenitzescu reaction) or benzofuran-2(3*H*)-ones (domino Blaise–Nenitzescu reaction).[16] In spite of these useful transformations, it is striking that quinones cannot make use of emblematic domino processes based on Michael addition/enolate capture.

We initiated our study with 3,5-dimethyl-2-benzoquinonyl boronic acid **1**, easily available by CAN oxidation of the corresponding dimethyl substituted 2,5-dimethoxy arylboronic acid, as previously reported.[10] The required 2-alkenyl indoles **2** and *N*-methyl-2-alkenyl indoles **3** were obtained via Wittig reaction from commercially available 1*H*-indole-2-carbaldehyde or *N*-methylindole-2-carbaldehyde respectively.[17−19] Reaction of **1** with 1*H*-2-(phenylvinyl)indole *E*-**2a** or 1*H*-2-(*o*-bromophenylvinyl)indole *E*-**2b** using CH_2Cl_2 (0.07 M) as solvent at rt gave compounds **4a** and **4b** respectively, resulting from 1,4-addition reaction of the indole to the quinone C-3 carbon, followed by protodeboronation (Scheme 2). Although yields were moderate, this result revealed that 2-alkenyl indoles could act as Michael type nucleophiles instead of as dienes in the reaction with **1**.[20]

To our delight, when *N*-methyl substituted (*E*)-2-[2-(*p*-methoxyphenyl)vinyl]indole (*E*)-**3a** was reacted with **1**, for 2 h at rt, compound **5a** was exclusively obtained (63% isolated yield) (Scheme 3). The formation of the twistenedienone **5a** must result from a domino sequence based on a 1,4-addition of the indole ring to the C-3 quinonyl boronic acid, followed by an IMDA/protodeboronation

(9) For recent examples of synthesis of isotwistanes by intramolecular [4 + 2] cycloaddition of a 1,3-cyclohexadiene moiety, see: (a) Zhang, G.-B.; Wang, F.-X.; Du, J.-Y.; Qu, H.; Ma, X.-Y.; Wei, M.-X.; Wang, C.-T.; Li, Q.; Fan, C.-A. *Org. Lett.* **2012**, *14*, 3696–3699 and references cited therein. (b) Zhao, C.; Zheng, H.; Jing, P.; Fang, B.; Xie, X.; She, X. *Org. Lett.* **2012**, *14*, 2293–2295. (c) Silva López, C.; Nieto Faza, O.; Rodríguez de Lera, A. *J. Org. Chem.* **2008**, 467–453.

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(14) For applications of a domino Diels–Alder/pyrolytic sulfoxide elimination sequence of 2-sulfinylquinones, see: (a) Urbano, A.; Carreño, M. C. *Org. Biomol. Chem.* **2013**, *11*, 699–708. (b) Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755–2757. (c) Carreño, M. C.; Garcia-Cerrada, S.; Sanz Cuesta, M. J.; Urbano, A. *Chem. Commun.* **2001**, 1452–1453. (d) Carreño, M. C.; Hernández-Sánchez, R.; Mahugo, J.; Urbano, A. *J. Org. Chem.* **1999**, *64*, 1387–1390.

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(16) (a) Chun, Y. S.; Ryu, K. Y.; Kim, J. H.; Shin, H.; Lee, S.-G. *Org. Biomol. Chem.* **2011**, *9*, 1317–1319. (b) Suryavanshi, P. A.; Sridharan, V.; Menéndez, J. C. *Org. Biomol. Chem.* **2010**, *8*, 3426–3436.

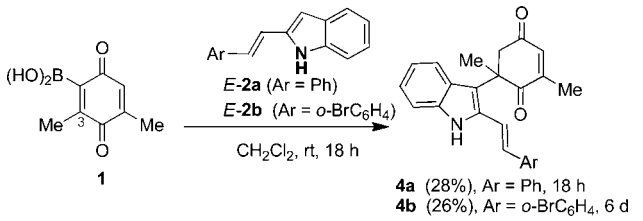
(17) For the synthesis of *N*-methylvinylindoles, see: (a) Masuda, K.; Ohmura, T.; Suginome, M. *Organometallics* **2011**, *30*, 1322–1325. (b) For the synthesis of 1*H*-vinylindoles, see: (c) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236–9239.

(18) *E*-Isomer of **3f** was exclusively obtained. Compounds *E*-**2a**, *E*-**2b**, and *E*-**3a** were obtained pure after column chromatography. Compounds **3b**–**d** were used as a mixture of *E*/*Z* isomers. For details, see Supporting Information.

(19) Stereoselective syntheses of *E*-vinylindoles based on Suzuki coupling have been reported: (a) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538–549. (b) Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G. *Synthesis* **2006**, 299–304.

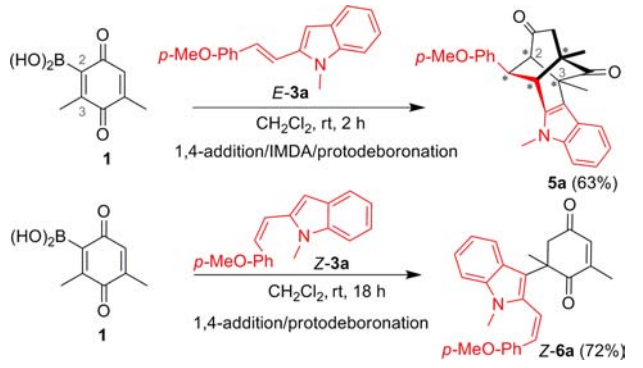
(20) For examples of 2-alkenyl indoles as dienes, see: (a) Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368–5374. (b) Abbiati, G.; Canevari, V.; Facoetti, D.; Rossi, E. *Eur. J. Org. Chem.* **2007**, 517–525 and references cited therein. (c) Pirovano, V.; Decataldo, L.; Rossi, E.; Vicente, R. *Chem. Commun.* **2013**, *49*, 3594–3596.

Scheme 2. Reaction of 1*H*-2-Alkenylindoles **2** with **1**



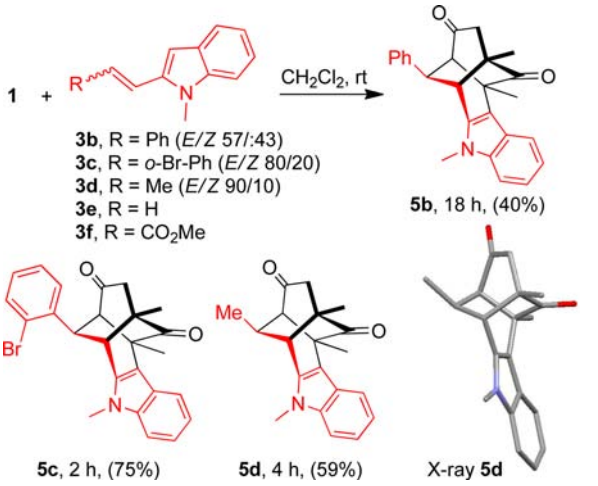
sequence,[21] where the alkenyl C-2 substituent at the indole is acting as a dienophile. In this process three new C−C bonds were formed as well as five stereogenic centers, two of them quaternary at the bridgehead carbons and with complete diastereoselectivity.

Scheme 3. Reaction of (*E*)-**3a** and (*Z*)-**3a** with **1**



The reaction of quinonyl boronic acid **1** with the pure (*Z*) isomer of *N*-methyl-2-[2-(*p*-methoxypheny)lvinyl]-indole (*Z*)-**3a** afforded, after 18 h, the 1,4-addition product (*Z*)-**6a** after protodeboronation in 72% yield (Scheme 3). This result indicated that the double bond geometry of the alkenyl substituent had a great influence on the second step of the domino sequence. We next examined the scope of this process by reacting boronic acid **1** with different 2-alkenylindoles (Scheme 4). Only the (*E*)-isomer of an inseparable 57/43 *E*/Z mixture of *N*-methyl-2-(2-phenylvinyl)-indole **3b** reacted with **1** affording the twistendione derivative **5b** in 40% isolated yield, after 4 h. Under these conditions, no 1,4-addition product was detected, and the (*Z*)-**3b** isomer was recovered unaltered.[22] 2-[2-(*o*-Bromophenyl)vinyl]-indole **3c** (*E*/*Z* 80:20) also reacted in 2 h at rt with quinonyl boronic acid **1**, to give twistane-like derivative **5c** in good yield (75%). Alkyl susbtituents on the dienophilic group of the *N*-methyl alkenyl indole were also able to give the domino process, as demonstrated in the reaction of *N*-methyl-2-propenylindole **3d** (90/10 *E*/*Z* mixture) with **1**. The structure of twistendione derivative **5d**, isolated in 59% yield, could be confirmed by X-ray diffraction (Scheme 4).[23] No 1,4-addition products were detected under these conditions, and *Z*-**3c** and *Z*-**3d** isomers remained unreacted.

Scheme 4. Reaction between **1** and *N*-Methyl-2-alkenylindoles **3b**−**f**, and X-ray Structure of Twistendione **5d**



N-Methyl-2-vinylindole **3e** did not deliver any appreciable reaction product in the presence of **1**, probably because of the instability of the starting 2-vinylindole in the reaction mixture. The reaction of **1** with the electron-poor methyl ester substituted alkenyl indole derivative (*E*)-**3f** did not occur, probably due to the diminished reactivity of this indole system toward the initial conjugate addition.

The formation of these twistane-like structures can be explained by the mechanism in Scheme 5. Initially, a FC alkylation of the indole ring occurs at the more electron-rich C-3 position of the heterocycle. The high electrophilicity of the C-3 methyl substituted quinonyl boronic acid allows this process to occur without external acidic catalysis. The initial 1,4-addition generates intermediate **A**, which can protonate and tautomerize to give **B**. Subsequent boron transfer from carbon to oxygen could afford the boron dienolate intermediate **C**. The IMDA reaction between the dienolate present in **C** and its dienophilic moiety would require a parallel disposition of both approaching partners, only possible if the C1′−C2′ double bond is situated out of the indole ring plane (**I** or **III** in Scheme 5). This out of plane disposition is probably forced by steric inhibition of resonance in the aromatic indole, due to the surrounding bulky *N*-Me group and the quaternary C-6 of the dienolate moiety. Moreover, the lack of reactivity of the *NH* alkenyl indoles **2** toward the IMDA process (Scheme 2) corroborates the essential role of the *N*-Me group in the second step of the domino sequence.[24] There are two possible regiochemical orientations of the dienophilic moiety that could lead a 6/6/6 twistane system (transition state **I**) or a 5/6/6 isomeric isotwistane

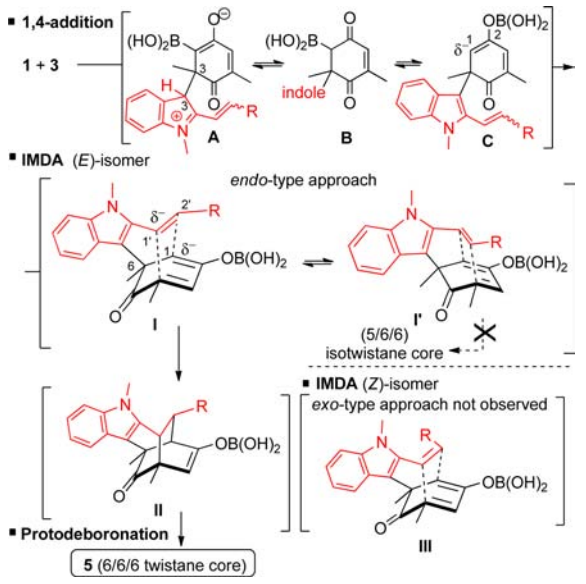
(21) See ref 10a for a similar protodeboronation step.

(22) Longer reaction times (18 h) gave a mixture of the twistenedione **5b**, together with the 1,4-addition compound resulting from (*Z*)-**3b** in a 71:29 ratio respectively.

(23) CCDC 952314 (**5d**): M_r $C_{20}H_{21}N_1O_2$. Unit cell parameters: *a* 10.4429(3) Å; *b* 11.4676(3) Å; *c* 14.1151(4) Å, space group *P*21/*c*.

(24) We could not disregard a faster protodeboronation than the IMDA, after the 1,4-addition step in *NH* alkenyl indoles reactions.

Scheme 5. Mechanistic Proposal: Regio- And Stereochemical Course of the Domino 1,4-Addition/IMDA/Protodeboronation Sequence of **1** and **3**



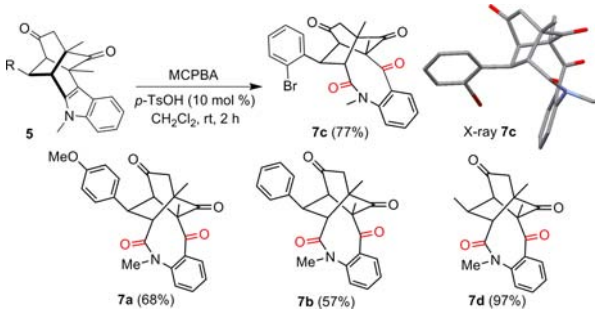
(transition state **I**′). The electron donating effect of the oxygenated substituent at C-2 of the diene increases the electron density (δ^-) at the vicinal C-1 carbon. Taking into account the exclusive formation of the 6/6/6 core after the protodeboronation step, the regiochemical course must be governed by the dienophile electron density distribution shown, leaving a (δ^-) at C-1′, which is favored by the electron-donating effect of the R alkenyl substituent (**I** in Scheme 5). The differences observed between the (*E*)- and (*Z*)-alkenyl indoles **3c** could originate from a favored *endo* approach of the (*E*)-alkenyl indole and a less favored IMDA *exo* approach of the (*Z*)-alkenyl pendant group, as shown in transition state **III** (Scheme 5).

Our results are complementary to the recent examples of intramolecular [4 + 2] cycloaddition between 2-trimethylsilyloxy-1,3-cyclohexadienes or simple 1,3-cyclohexadienes with a pendant terminal 6-alkenyl substituent, where a 5/6/6 isotwistane nucleus is reported to be formed in the IMDA reaction.[9] The C-2 boronic acid substituent at **1** is essential for the regiocontrol of the initial 1,4-addition process and to generate a useful dienolate.

Finally, taking advantage of the indole framework present in the twistenedione structures **5**, we could achieve the synthesis of expanded novel 6/6/9 tricyclic systems through a Witkop type oxidation[25] promoted by *m*-CPBA and catalytic *p*-TsOH. Under the conditions shown in

(25) (a) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, *73*, 2641–2647. (b) Mentel, M.; Breinbauer, R. *Curr. Org. Chem.* **2007**, *11*, 159–176.

Scheme 6. Synthesis of 6/6/9 Cage **7** from **5** and X-ray of **7c**



Scheme 6, compounds **5a**–**d** evolved, through the oxidative cleavage of the C-2–C-3 indole bond, to the 9-membered ring ketolactam derivatives **7a**–**d** in good to excellent yields. The structure of **7c** was confirmed by X-ray diffraction.[26] This method opens an easy approach to such derivatives in only two steps.

In summary, we have reported a direct synthesis of 6/6/6 cage-shaped substituted twistanediones by reaction between 3,5-dimethyl substituted-2-quinonyl boronic acid and (*E*)-2-alkenylindoles. The synthesis is based on a 1,4-addition/IMDA/protodeboronation domino sequence. The presence of the boronic acid in the quinone promotes a regioselective 1,4-addition, giving a reactive dienolate. Appropiate charge distribution in the diene and dienophile is essential to direct the regiochemical course of the IMDA process and leads to the formation of unique twistane-like structures. Analogue systems lacking this charge distribution gave the isotwistane framework. A successful synthetic extension of this method involves oxidative cleavage of the indole ring to expand 6/6/9 membered ring containing cage compounds.

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Supporting Information Available. Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and cif files of **5d** and **7c**. This material is available free of charge via Internet at http://pubs.acs.org.

(26) CCDC 952315 (**7c**): M_r $C_{25}H_{22}BrN_1O_4$. Unit cell parameters: *a* 8.0904(2) Å; *b* 27.0158(7) Å; *c* 9.5814(2) Å, space group $P21/c$.

The authors declare no competing financial interest.