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Divergent Total Syntheses of Isobatzellines A/B and Batzelline A

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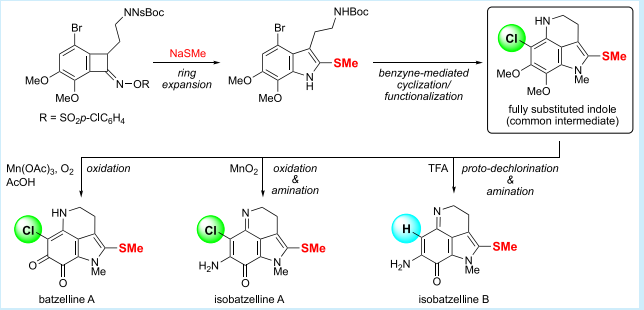
ABSTRACT: Divergent total syntheses of isobatzellines A/B and batzelline A were accomplished. A fully substituted common indole intermediate bearing C-2 methylthio and C-5 chloro groups was constructed via ring expansion of benzocyclobutenone oxime sulfonate with NaSMe and a benzyne-mediated cyclization/functionalization sequence as the key steps. The total synthesis of isobatzelline B was achieved via formation of the iminoquinone structure by the redox-neutral acid-promoted C-5 proto-dechlorination of the common indole intermediate. The total syntheses of isobatzelline A and batzelline A were completed in a divergent manner by oxidation of the common indole intermediate using MnO_2 or $Mn(OAc)_3$, respectively.



Marine alkaloids with the pyrrolo[4,3,2-*de*]quinoline skeleton, such as isobatzellines,[1,2] batzellines,[1−3] and makaluvamines,[4] have received a great deal of attention in the fields of drug discovery and organic synthesis owing to their broad range of biological activities and characteristic structures (Figure 1). For example, isobatzellines and batzellines isolated

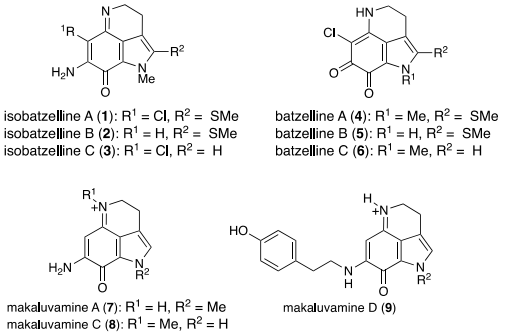


Figure 1. Isobatzellines, batzellines, and makaluvamines

from deep-water Caribbean sponge *Batzella* sp. exhibit cytotoxic activity against P388 leukemia cells, and the latter compounds inhibit HIV-1 envelope-mediated cell fusion.[2] Furthermore, makaluvamine A exhibits potent *in vitro* cytotoxicity against the human colon tumor cell line HCT116 and inhibitory activity against topoisomerase II.[4a] Accordingly, tremendous effort has been devoted to develop reliable synthetic routes for construction of the highly functionalized pyrrolo[4,3,2-*de*]quinoline skeleton, and several total syntheses have been reported.[5−7] However, synthetic routes to isobatzellines A (**1**) and B (**2**) and batzellines A (**4**) and B (**5**) bearing the C2-methylthio group have not been fully explored, and their total syntheses have only been reported by Joule's group.[8,9] As part of our ongoing interest in the total synthesis of pyrroloquinoline alkaloids,[5d,10] we herein report efficient and divergent total syntheses of **1**, **2**, and **4** featuring three key processes, including the ring expansion of benzocyclobutenone oxime sulfonate with NaSMe to construct 2-methylthioindole,[11] a benzyne-mediated cyclization/functionalization cascade to form the tetrahydroquinoline ring,[12] and a Mn-reagent-dependent oxidative formation of iminoquinone and *o*-benzoquinone.

There are two major synthetic challenges to overcome in the construction of batzellines and isobatzellines family compounds. One is adjusting the oxidation state of the pyrrolo[4,3,2-*de*]quinoline skeleton in the latter stage of the synthesis without affecting the electron-rich indole skeleton. The other is the construction of a fully substituted indole skeleton with the introduction of oxygen, nitrogen, sulfur, and halogen substituents at the requisite positions. These issues are made more challenging by the presence of the oxidant-labile methylthio group. In Joule's pioneering total synthesis of **2**,[8,9] oxidation of 2-methylthioindole **12** was executed in the final step to provide pyrroloiminoquinone **13** in only 30% yield, whereas the C-2-unsubstituted indole **14** gave pyrroloiminoquinone **15** in high yield under the same oxidation conditions (Scheme 1a). For the total syntheses of **1** and **4**, C-5 chlorination of indole **16** was attempted (Scheme

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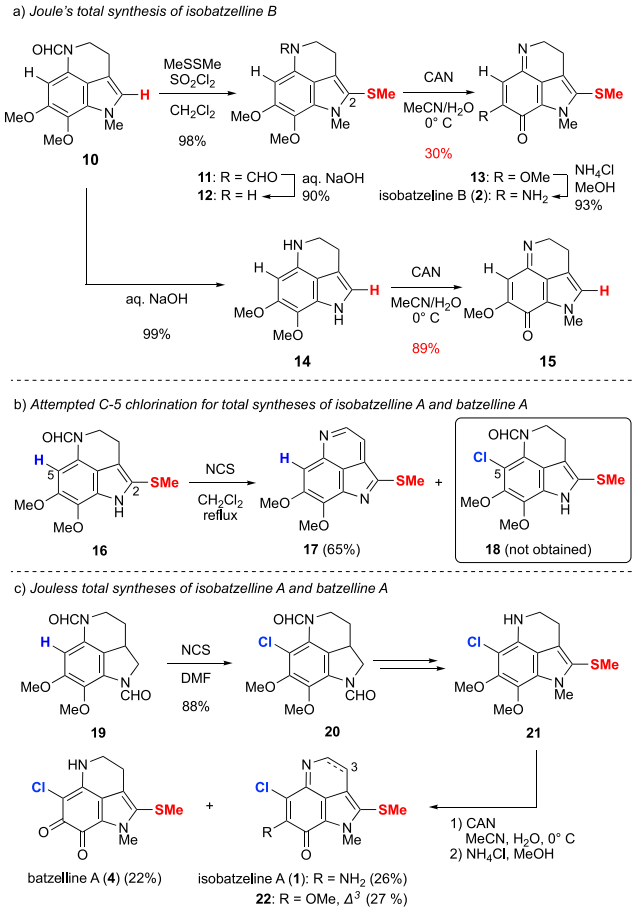
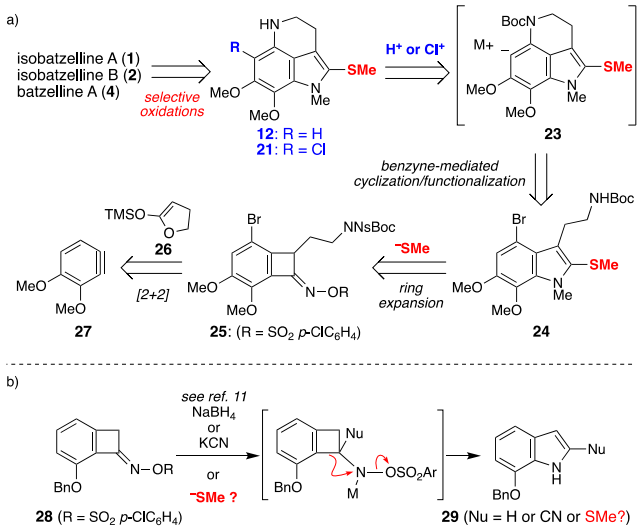
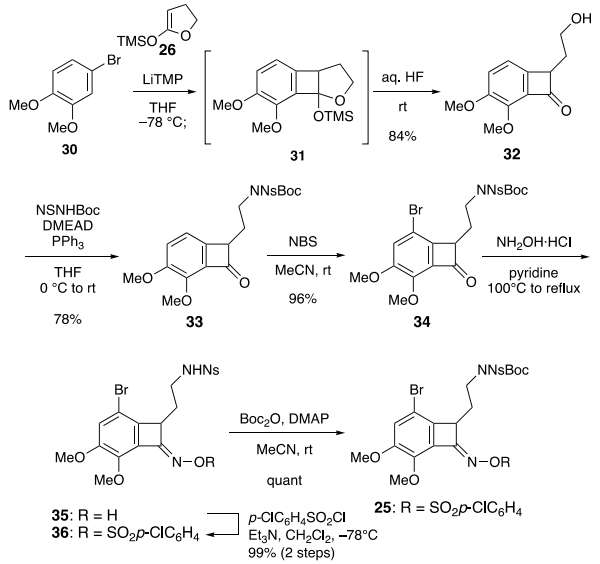
Scheme 1. Joule's Total Syntheses of Isobatzellines A (1) and B (2) and batzelline A (4)



Scheme 2. Retrosynthetic Analysis



Scheme 3. Synthesis of Oxime Sulfonate 25



1b). However, reaction with NCS only provided the fully aromatized compound **17**, presumably triggered by undesired *S*-chlorination of the methylthio group. Although this undesired aromatization was bypassed by the early stage of C-5 chlorination prior to sulfenylation, oxidation of **21** to pyrroloiminoquinone in the final step was also not straightforward, and a mixture of isobatzelline A (26%), batzelline A (22%), and aromatized product **22** (27%) was obtained after one-pot amination (Scheme 1c).

With these synthetic issues in mind, we conducted retrosynthetic analysis (Scheme 2). We set indoles **12** and **21** as precursors of isobatzellines A (**1**), B (**2**), and batzelline A (**4**) hoping that mild and methylthio-group-compatible oxidation conditions could be identified. Chlorination or protonation of the aryl anion species **23** generated by our benzyne-mediated cyclization/functionalization protocol using 4-bromoindole **24** would provide **12** or **21**, respectively.[10] For construction of the highly substituted 2-methylthioindole, we planned to expand the scope of our indole synthesis using the ring expansion of benzocyclobutenone oxime sulfonate developed in the course of our synthetic studies on (+)-CC-1065. Thus, based on our ring-expansion reaction of oxime sulfonates with hydride and cyanide ion sources (Scheme 2b),[11] we envisaged that 1,2-addition of methanethiolate to oxime sulfonate **25** followed by ring expansion with concomitant *N*-*O* bond cleavage would provide 2-methylthioindole **24**.[13] Oxime sulfonate **25** should be easily accessible via regioselective [2 + 2] cycloaddition of benzyne **27**[14] and ketene silyl acetal **26**.[15]

Our synthesis commenced with the [2 + 2] cycloaddition of ketene silyl acetal **26** and the benzyne species **27** generated from 4-bromoveratrole **30** by treatment with LiTMP, which provided benzocyclobutenone **32** with perfect regioselectivity after HF-mediated ring opening of tricyclic adduct **31** (Scheme 3). The resultant primary alcohol **32** was converted to Ns amide **33** under Mitsunobu conditions using NsNHBoc[16] and DMEAD.[17] Bromination of **33** followed by condensation of the resultant bromide **34** with hydroxylamine at high temperature (100−130 °C) with undesired loss of the Boc group gave oxime **35**.[18] Finally, sulfonylation of oxime **35** and subsequent Boc protection furnished the desired oxime sulfonate **25**.[18]

Given the highly strained oxime sulfonate **25**, we focused on the key ring-expansion reaction triggered by nucleophilic addition of thiolate. First, **25** was treated with NaSMe (5.0 equiv) in DMSO or DMF at room temperature based on our

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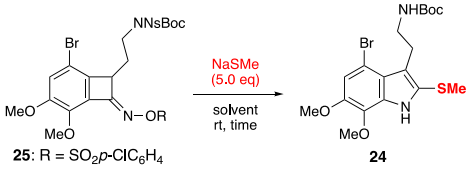
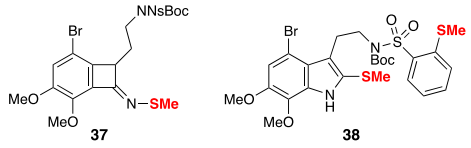
previously established conditions.[11] The expected reaction and concomitant removal of the Ns group proceeded to give indole **24** and a small amount of side product **38** due to *ipso* substitution on the Ns group (Table 1, entries 1 and 2).[19]

Table 1. Ring-Expansion Reaction of 25





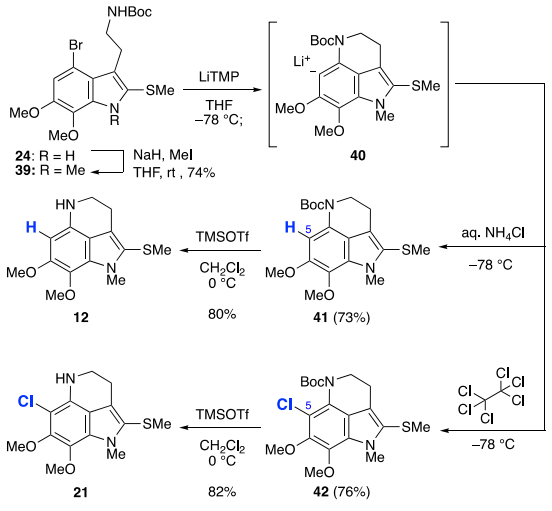
entry	solvent[a]	time (h)	**24** (%)[b]	**37** (%)[b]	**38** (%)[b]
1	DMSO	3.5	56	–	<9[c]
2	DMF	4.5	45	–	<17[c]
3	THF	2	49	–	–
4	CH_2Cl_2	3	42	–	–
5	MeOH	23	–	44	–
6	MeCN	1.5	86	–	trace

[a]0.1 M concentration. [b]Isolated yield. [c]Isolated with trace amount of inseparable unidentified byproducts.

Switching solvent to THF or CH_2Cl_2 did not increase the yield of **24** (Table 1, entries 3 and 4), while reaction in MeOH did not afford indole **24** at all, instead providing thiooxime **37** due to substitution on the oxime sp^2 nitrogen atom (Table 1, entry 5).[20] Further screening revealed that MeCN was the best choice of solvent, providing **24** as the sole product in high yield (86%) (Table 1, entry 6).

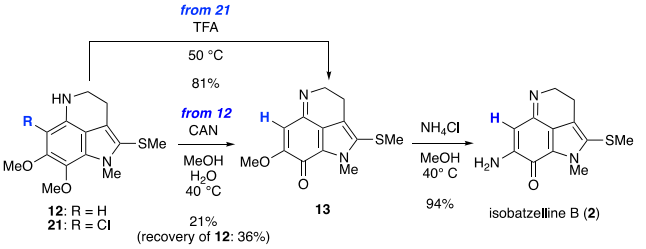
Having established a new protocol for construction of 2-methylthioindole, we then constructed the fully substituted piperidine ring-fused indole skeletons **12** and **21** by our benzyne-mediated cyclization/functionalization protocol (Scheme 4). After *N*-methylation of indole **24**, the resultant compound **39** was treated with excess LiTMP to promote the benzyne generation/cyclization cascade that provides the pivotal aryl anion species **40**. Aqueous workup of the reaction mixture with aq. NH_4Cl afforded the C-5-unsubstituted indole **41**, whereas addition of hexachloroethane to the reaction mixture gave 5-chloroindole **42**. Finally, the Boc group was removed to afford pyrroloindoles **12** and **21**, respectively.[21]

Scheme 4. Syntheses of Indoles 12 and 21



With pyrroloindoles **12** and **21** in hand, we focused on the crucial oxidative skeletal transformation toward isobatzellines A (**1**) and B (**2**) and batzelline A (**4**). Based on Joule's total synthesis of isobatzelline B (2), C5–H indole **12** was treated with CAN to afford the desired pyrroloiminoquinone **13**. However, as anticipated, the yield was very low (Scheme 5).

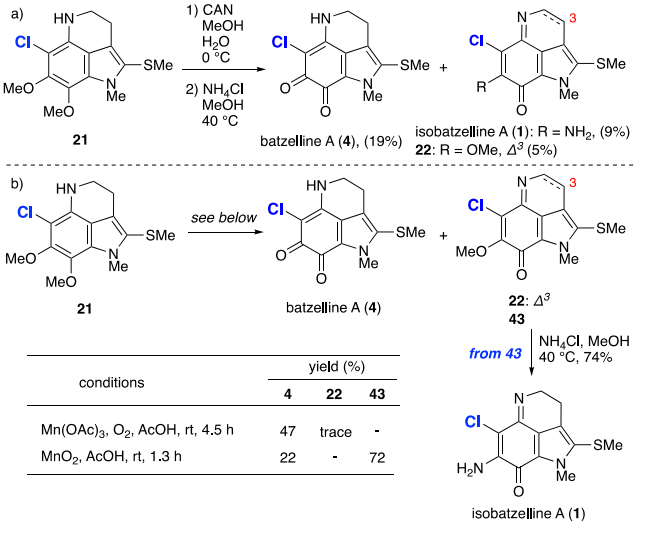
Scheme 5. Total Synthesis of Isobatzelline B (2)



Instead, we found another way to obtain pyrroloiminoquinone **13** from C-5 chloroindole **21**. Upon subjection of C-5 chloroindole **21** to TFA at 50 °C, dechlorinative pyrroloiminoquinone formation occurred to afford **13** in 81% yield. This is a Brønsted acid promoted redox-neutral proto-dechlorination process because C-5 chloroindole **21** has the same formal oxidation state as **13**.[22] The total synthesis of isobatzelline B (**2**) was achieved by introduction of an amino group by addition–elimination reaction.

Next, the final stage of isobatzelline A (**1**) and batzelline A (**4**) synthesis was carefully investigated. As reported, CAN oxidation/amination treatment of **21** resulted in low yields of batzelline A (**4**) and isobatzelline A (**1**) and many byproducts, such as the fully aromatized compound **22** (Scheme 6a). In sharp contrast, we successfully established a switchable oxidation protocol to selectively provide isobatzelline A (**1**) or batzelline A (**4**) depending on the manganese oxidant

Scheme 6. Total Syntheses of Isobatzelline A (1) and Batzelline A (4)



conditions	yield (%) 4	22	43
$Mn(OAc)_3$, O_2, AcOH, rt, 4.5 h	47	trace	-
MnO_2, AcOH, rt, 1.3 h	22	-	72

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reagent used. Thus, treatment of indole **21** with $Mn(OAc)_3$ in AcOH under an O_2 atmosphere afforded batzelline A (**4**) in acceptable yield along with a trace amount of **22** (Scheme 6b).[23] Conversely, reaction using MnO_2 in AcOH gave pyrroloiminoquinone **43** as the main product in high yield, which was then converted to isobatzelline A (**1**) by introduction of an amino group (Scheme 6b).

In summary, divergent total syntheses of isobatzellines A and B and batzelline A were accomplished by the rapid assembly of the highly substituted pyrrolidine-fused common 2-methylthioindole by ring expansion reaction of benzocyclobutenone oxime sulfonates with NaSMe and a benzyne-mediated cyclization/functionalization protocol. The total synthesis of isobatzelline B was achieved via TFA-promoted protodechlorination of the common intermediate. Selective derivatization to isobatzelline A and batzelline A was made possible by the manganese-oxidant-dependent oxidation of piperidine-fused 2-methylthioindole to the benzoquinone or iminoquinone derivative. To the best of the authors' knowledge, this is the first report of the use of manganese reagents for the highly chemoselective oxidative transformation of electron-rich indole skeletons to the pyrrolo[4,3,2-*de*]quinoline skeleton. The efficiencies of our total syntheses are demonstrated by the dramatically improved total yields of the products compared to those achieved in previous total syntheses,[9] i.e., isobatzelline A yields from 0.51% to 13%, isobatzelline B yields from 2.3% to 19%, and batzelline A yields from 1.1% to 12%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01894.

Full experimental procedure; ^1H and ^{13}C spectra of compounds **1**, **2**, **4**, **12**, **13**, **21**, **24**, **25**, **32**, **33**, **34**, **36**, **37**, **38**, **39**, **41**, **42** (PDF)

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Notes

The authors declare no competing financial interest.

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