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Total Synthesis of (–)-Nahuoic Acid C_i (B_{ii})

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Abstract

A convergent total synthesis of (–)-nahuoic acid C_i(B_{ii}) (**3**), a novel *cis*-decalin polyketide has been achieved. Key synthetic transformations include Type II Anion Relay Chemistry (ARC) to construct the polyol chain, a Ti-catalyzed asymmetric Diels-Alder reaction to generate the *cis*-decalin skeleton, and a latestage large fragment union exploiting a Micalizio alkoxide-directed alkyne-alkene coupling tactic.

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Nahuoic acid A (**1**; Figure 1), isolated by Anderson and coworkers in 2013 from a culture of a *Streptomyces* sp. obtained from a tropical marine sediment, displays selective (S)-adenosylmethionine (SAM)-competitive inhibitor activity against the histone lysine methyltransferase¹ SETD8 enzyme.² In 2016, the same group reported the isolation of nahuoic acids B_i-E_i (**2**, **3**, **5**, and **6**), which exhibit similar inhibitory effects on SETD8.³ In the same year, the Qi group independently reported the isolation of four related congeners,

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ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, as well as spectroscopic and analytical data for all new compounds (PDF)

X-ray data for compound (+)-**8** (CIF)

X-ray data for compound (–)-**11** (CIF)

X-ray data for compound (–)-**30** (CIF)

The authors declare no competing financial interests.

the nahuoic acids B_{ii}-E_{ii} (**3**, **4**, **5**, **7**),⁴ leading to a total of seven members of this architecturally intriguing family of polyketide acids. Herein, we reported the first total synthesis of a member of the nahuoic acid family, namely C_i(B_{ii}) (**3**).

The nahuoic acids (**1–7**) feature highly functionalized *cis*-decalin motifs in conjunction with polyol side chains. From the retrosynthetic perspective, we envisioned that a disconnection between C(13) and C(14), exploiting a Micalizio alkyne-alkene union protocol,⁵ would permit a unified convergent approach to the nahuoic acids and their potential analogues (Scheme 1). Such a disconnection would lead to two major fragments *cis*-decalin **8** and acetylene **9**. We also note that the nahuoic acids differ specifically in the hydroxylation patterns at C(7) and C(8) of the *cis*-decalin motif. To permit facile adjustment at these stereogenic centers, we targeted enone **10** as a common intermediate, which would hold the promise of access to the various decalin skeletons, via dihydroxylation leading to nahuoic acid **3**, epoxidation-ring opening to furnish nahuoic acids **1,2,5** and **6**, and via hydrogenation for nahuoic acids **4** and **7**. Importantly, for nahuoic C_i(B_{ii}) (**3**), as illustrated in Scheme 1, dihydroxylation of **10** can be envisioned to occur from the convex face, leading to the most functionalized nahuoic decalin structural fragment (**8**) possessing eight contiguous stereogenic centers. Enone **10** in turn would derive from **11**, which would be constructed via an asymmetric Diels-Alder reaction between quinone **12** and diene **13**. Also of note, the nahuoic acids differ in the length and functionality of their polyol side chains, featuring either 1,3,5-triols or 1,3,5,7-tetrols. Such advanced intermediates in turn would appear readily accessible via Anion Relay Chemistry (ARC),⁶ an efficient, multicomponent union protocol developed in our Laboratory. For example, side chain **9** possessing the 1,3,5-triol functionality could be constructed via a Type II ARC tactic employing bifunctional linchpin **16** recently introduced by our group.^{6e}

We chose to initiate the synthesis of nahuoic acid C_i(B_{ii}) (**3**) with construction of the 1,3,5-triol side chain **9** employing the ARC tactic outlined in Scheme 2. In one-flask, employing isopropyl lithium (**15**), linchpin (+)-**16** and (*R*)-(-)-epichlorohydrin [(-)-**17**], the three-component adduct (+)-**14** was constructed in 76% yield on five-gram scale with excellent diastereoselectivity (>20:1). This ARC process was initiated by nucleophilic attack of isopropyl lithium (**15**) to linchpin (+)-**16**. A [1,4]-Brook rearrangement⁷ was in turn triggered by the addition of HMPA to relay the negative charge via silyl group migration from carbon C(1) in **18** to oxygen in **19**. Carbanion **19** was then trapped with (*R*)-(-)-epichlorohydrin [(-)-**17**] to complete the one-flask construction process. Adduct (+)-**14** was then subjected to dithiane removal with simultaneous hydrolysis of the TMS ether to provide ketone (+)-**21**.⁸ Chelation controlled reduction of (+)-**21** furnished *syn*diol (+)-**22**,⁹ which was protected as an acetonide to provide (+)-**23**.¹⁰ Epoxide ring opening of (+)-**23** at the terminal position with propynyl-lithium in the presence of BF₃•THF¹¹ and final protection as the methoxymethyl (MOM) ether¹² completed construction of the alkyne side chain (+)-**9** in a total of six flasks in 30% overall yield.

We turned next to construction of the requisite *cis*-decalin **8**, exploring a Lewis acid catalyzed asymmetric Diels-Alder reaction (Scheme 3). Thermal cycloaddition between **12**^{13,14} and **13**¹⁵ led to the desired chemo- and regio-selective isomer (±)-**11**. Encouraged by

this initial Diels-Alder success, we turned to a series of Lewis acids¹⁶ to achieve enantioselectivity. Titanium-complex (–)-**25**,^{17,18} possessing the 1-naphthyl substituted TADDOL ligand, was identified to furnish the optimal enantioselectivity (*ca.* 73% *ee*), when employing 1 eq. Interestingly, we discovered that addition of 4 Å molecular sieves reduced the required loading of Lewis acid to 20 mol%. Further optimization including temperatures and solvents afforded the desired enantiomer (–)-**11** in 95% yield with 86% *ee*. The enantiomeric excess of **11** could then be further enriched equal to or higher than 98% (determined by chiral SFC) by crystallization. The absolute configuration (–)-**11** was established via single crystal X-ray analysis.

With highly enantio-enriched intermediate (–)-**11** in hand, we proceeded to complete construction of *cis*-decalin **8** for the proposed Micalizio union (Scheme 4 and 5). Intermediate (–)-**11** was first subjected to exhaustive reduction with LiAlH₄, followed by acid-mediated hydrolysis with concomitant elimination to provide enone (–)-**26**.¹⁹ The secondary hydroxyl in (–)-**26** was then protected as a TBS ether to furnish (–)-**10**. Although we encountered difficulties to dihydroxylate selectively the desired C(2,3) double bond in (–)-**10**, the enone olefin C(6,7) could first be reduced by selective hydrogenation to yield (+)-**27**, which was then dihydroxylated²⁰ from the convex face to furnish the requisite diol (+)-**28**. Upon protection of the diol as acetone (+)-**29**,²¹ the enone functionality in (–)-**30** was then efficiently regenerated via a Pd(OAc)₂ catalyzed Saegusa–Ito oxidation.²²

We next employed a CuBr•DMS-mediated vinyl conjugate addition²³ to (–)-**30** from the convex face to provide ketone (+)-**31**, which was subjected to the formation of vinyl triflate (+)-**32** and subsequently to cross coupling^{24,25} with methylmagnesium bromide to furnish diene (+)-**33** in a combined yield of 53% (Scheme 5). Upon careful hydrolysis of the TBS ether with TBAF at 60 °C, *cis*-decalin fragment (+)-**8**, the second union partner was now available in a total of 11 steps in 15% overall yield from (–)-**11**. The relative and absolute stereostructures of (–)-**30** and (+)-**8** were confirmed by X-ray analysis (Scheme 4 and 5).

Having arrived at the requisite decalin (+)-**8** and alkyne (+)-**9**, we initiated studies on their union employing the alkoxide directed alkyne-alkene coupling tactic developed by Micalizio and coworkers (Scheme 6).^{26–28} This tactic begins with the generation of Tialkyne complex^{29,30} **34** by treatment of (+)-**9** with TiCl(O*i*-Pr)₃ and Grignard reagent *c*-C₅H₉MgCl. In a separate flask, the allylic hydroxyl in decalin (+)-**8** is deprotonated with *n*-BuLi in toluene. The resulting lithium alkoxide **35** is then introduced to the flask containing Ti-alkyne complex **34** to direct approach from the concave face, leading to the desired stereochemistry at C(13) in (–)-**36**. Importantly, the desired regioselectivity is also achieved to furnish the trisubstituted *E*-alkene between C(14) and C(15), presumably due to minimization of the steric hindrance between the methyl group with the decalin *vis-a-vis* the methylene group. Pleasingly, this alkoxide directed union between the two fragments [(+)-**8** and (+)-**9**] furnished adduct (–)-**36** in 61% yield.

The endgame to complete the total synthesis of nahuic acid C₁(B₁₁) (**3**) now only required selective installation of the unsaturated carboxylic acid moiety to the terminal olefin, and then global deprotection (Scheme 7). Olefin metathesis between (–)-**36** and methyl methacrylate in the presence of Hoveyda-Grubbs II catalyst produced the a,b-unsaturated

methyl ester (–)-**37** with correct geometry.^{31,32} The fully protected intermediate (–)-**37** was then subjected to mild LiBF₄ mediated hydrolysis to reveal the six hydroxyl groups,^{33,34} and in turn saponification with LiOH to complete the total synthesis of (–)-nahuic acid C_i(B_{ii}) [(–)-**3**].

The spectral data for (–)-nahuic acid C_i(B_{ii}) was independently reported by both the Anderson and Qi groups, with the major difference observed in ¹H NMR between 4.0–4.5 ppm, corresponding to the six hydroxyl proton resonances. Pleasingly, initial 500 MHz ¹H NMR spectra of totally synthetic material displayed excellent agreement with that derived from the natural product as reported by Qi and coworker.⁴ Upon addition of a trace amount of deuterated TFA to the NMR sample, the six exchangeable proton resonances could no longer be distinguished in ¹H NMR,² resulting in NMR spectral properties (500 MHz ¹H and 125 MHz ¹³C) identical with that published by Anderson and coworkers.³ Other spectral properties (i.e., HRMS parent ion identification and chiroptical properties) of synthetic nahuic C_i(B_{ii}) [(–)-**3**] were also in total agreement with that published by both the Qi and Anderson groups.

In summary, we have achieved the first total synthesis of a member of the nahuic acid family of *cis*-decalin-containing polyketides, namely C_i(B_{ii}) [(–)-**3**], in a longest linear sequence of 16 steps. Highlights of the synthesis include Type II Anion Relay Chemistry (ARC) to construct the polyol chain, a Ti-catalyzed asymmetric Diels-Alder reaction to generate the *cis*-decalin skeleton in a highly enantiomerically enriched form, and a late-stage strategic large fragment union via the Micalizio alkoxide-directed alkyne-alkene tactic. Studies toward the synthesis of other members of the nahuic acid family, as well as the development of analogues for biological evaluations continue in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
 Structures of Nahuoic Acids

Scheme 1.
Retrosynthetic Analysis of Nahuic Acids

Scheme 2.
Synthesis of Side Chain (+)-9 via Type II ARC

Conditions

1. Toluene/CH₂Cl₂, 120 °C, 48 h
2. 1 eq. **25**, CH₂Cl₂, – 40 °C, 24 h
3. 20 mol% **25**, CH₂Cl₂, 0 °C to rt, 24 h
4. 20 mol% **25**, 4 Å MS, CH₂Cl₂, – 60 °C, 12 h
5. 20 mol% **25**, 4 Å MS, toluene, –78 to – 40 °C, 42 h

Results

74%, racemic
 71%, 73% ee
 25%, 55% ee
 80%, 71% ee
 95%, 86% ee

Ti-complex **(–)-25**

Scheme 3.
 Ti-Catalyzed Asymmetric Diels-Alder Reaction

Scheme 4.
Synthesis of Intermediate (-)-30

Scheme 5.
Synthesis of *Cis*-Decalin (+)-8

Scheme 6.
Hydroxyl-Directed Alkyne-Alkene Coupling

Scheme 7. Endgame Strategy towards the Completion of (-)-Nahuoic Acid C_i(B_{ii}).