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Total Synthesis of (−)-Mitrephorone A Enabled by Stereoselective Nitrile Oxide Cycloaddition and Tetrasubstituted Olefin Synthesis

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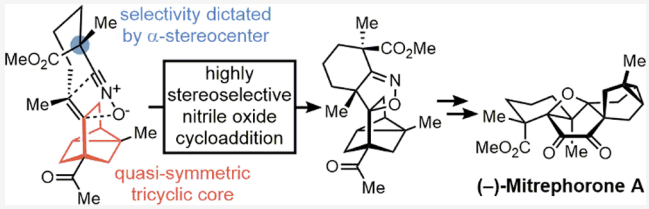
ABSTRACT: A highly enantioselective and diastereoselective total synthesis of the diterpenoid (−)-mitrephorone A is presented. Key to the synthesis are stereocontrolled 1,4-semi-hydrogenation of a 1,3-diene to a tetrasubstituted double bond, enzyme-catalyzed malonate desymmetrization, and highly diastereoselective nitrile oxide cycloaddition. The streamlined strategy is a considerable improvement to those reported earlier in terms of diastereo- and enantioselectivity. For the first time, the combination of modern Pd-cross-coupling with Cr-catalyzed reduction allows for rapid access to tetrasubstituted olefins with full stereocontrol.



INTRODUCTION

(−)-Mitrephorone A (**1**) is a trachylobane natural product characterized by a pentacyclic carbon skeleton, which includes a tricyclo[3.2.1.0^{2,7}]octane (Scheme 1).[1,2] The carbon framework of **1** encompasses at the core a unique fully substituted oxetane. Its five contiguous stereocenters along with its complex caged structure render **1** a formidable target for stereoselective synthesis.[3,4] In addition to synthetic challenges, (−)-mitrephorone A (**1**) exhibits cytostatic activity against a number of bacterial and fungal pathogens as well as cytotoxicity against selected cancer cell lines (MCF-7, H460, SF-268).[1,2,5]

We have previously reported the first and enantioselective total synthesis of (−)-mitrephorone A (**1**), which lacked diastereocontrol.[3] Herein, we report a new route for a highly enantio- and diastereoselective synthesis of **1**. Our retrosynthetic analysis involved disconnection of (−)-mitrephorone A (**1**) to **2** (Scheme 1). The 1,3-relationship of ketone and tertiary alcohol in **2** is a partial retron for a nitrile oxide cycloaddition strategy via isoxazoline **3**.[6] We wondered whether the stereogenic center α to the nitrile oxide in **4** would lead to control over facial selectivity in an intramolecular dipolar cycloaddition reaction (**4** → **3**). A key requirement of this approach is the stereoselective synthesis of the tetrasubstituted olefin embedded in **4**. Although traditional approaches to such an olefin might feature condensation reactions of the corresponding tricyclic ketone, we envisioned a different strategy involving diene **5**. At the outset, it was not clear how we would control the configuration of a tetrasubstituted olefin. The approach we describe reveals an effective solution to the synthesis of tetrasubstituted olefins, enabling diastereoselective functionalization of chiral tricyclo-[3.2.1.0^{2,7}]octanes and related structures. More broadly, the new retrosynthetic plan outlined in Scheme 1 leads to novel stereodefined strategies to the caged structure of (−)-mitrephorone A (**1**) and other trachylobanes.

The successful use of olefin **4** in our synthesis requires control over both facial selectivity and olefin geometry. To address the former, we conceived of an approach involving an intramolecular annulation reaction. The strategic design of precursors such as **9** includes a resident stereogenic center (*) along the connecting backbone as a stereochemical controlling feature (Scheme 2). In addressing the latter, it is important to note that addition reactions to tetrasubstituted olefin **9** set two stereocenters, and olefin geometry dictates their relative configuration ((*E*)-**9** → **10** vs (*Z*)-**9** → **11**).

RESULTS AND DISCUSSION

Olefin Synthesis. There are numerous methods available for ketone olefination en route to **4** (Scheme 1). In our initial studies, we tested several approaches for olefin synthesis from tricyclo[3.2.1.0^{2,7}]octanone **12** (Scheme 3).[7] The tetrasubstituted alkenes we envisioned synthesizing feature two structural elements that render their stereoselective synthesis challenging: (1) They include an allylic quaternary center, which can reduce reactivity of olefin precursors, and (2) methyl and methylenes at one end of the olefin can be sterically challenging to differentiate when controlling olefin geometry. Initial attempts employing Wittig and Horner−Wadsworth−Emmons olefinations[8] as well as McMurry

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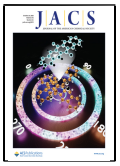

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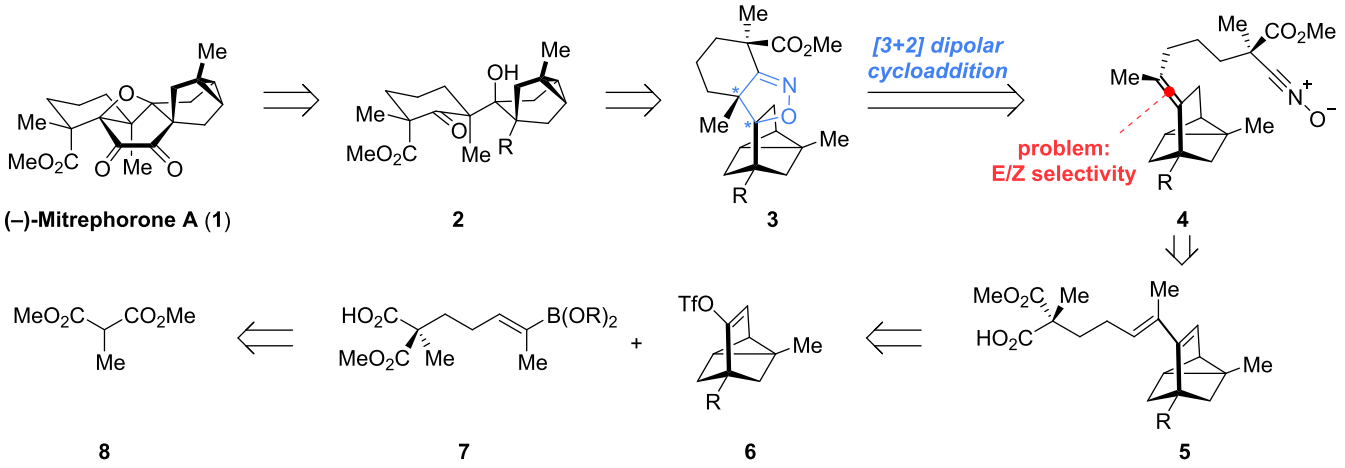
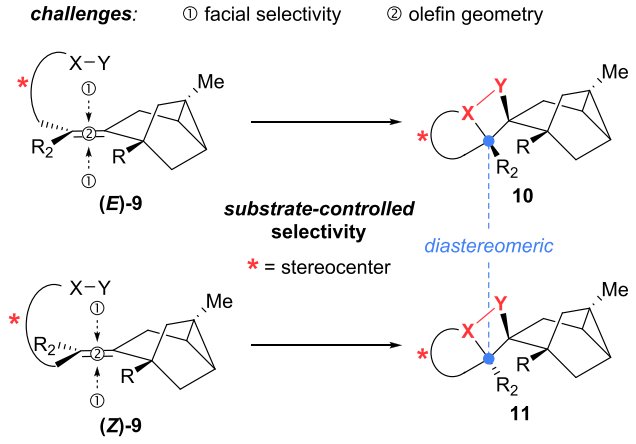
Scheme 1. (−)-Mitrephorone A (1) and Retrosynthetic Analysis



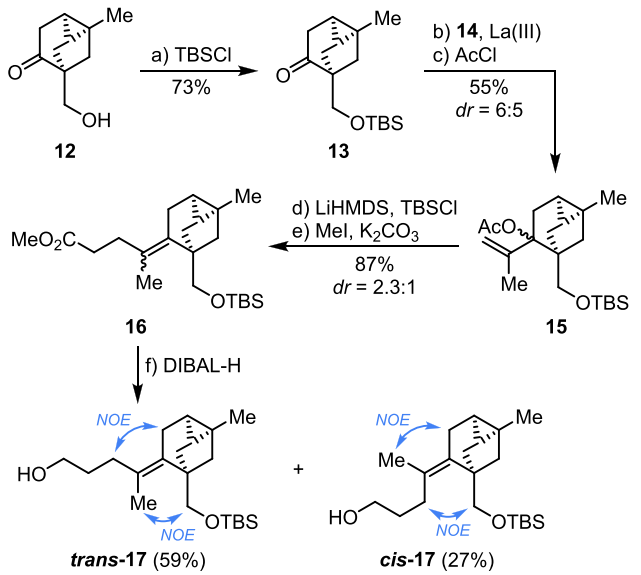
couplings[9] did not afford any tetrasubstituted olefins. Claisen rearrangements have been previously employed in the stereoselective synthesis of tetrasubstituted alkenes.[10] To this end, we transformed hydroxyketone **12** (95% *ee*) into allylic acetate **15** in three steps and 40% yield as 1.2:1 mixture of diastereomers (Scheme 3). Ireland−Claisen rearrangement was induced by treatment of **15** with LiHMDS, TBSCl, and HMPA,[11] and after treatment with methyl iodide and potassium carbonate, ester **16** was obtained in 87% yield as a 2.3:1 mixture of diastereomers. After reduction using DIBAL-H, the two double bond isomers were separated and assigned via 2D NOESY NMR experiments (see the Supporting Information (SI) for details). Further attempts to optimize the diastereoselectivity in the Ireland−Claisen reaction by employing different silyl groups did not lead to improvement. As we opted for a highly stereoselective synthesis, we subsequently envisioned different routes to the tetrasubstituted olefin not involving nucleophilic addition to tricyclic ketones.

Stereocontrolled preparation of tetrasubstituted olefins has been a longstanding challenge in organic synthesis.[8,12] A conceptually new route to tetrasubstituted olefin **4** would require stereoselective reduction of the diene in **5** in a catalyst-controlled process (Scheme 1). 1,3-Dienes may be conveniently accessed via palladium-catalyzed sp^2−sp^2 cross-coupling.

Scheme 2. Stereochemical Considerations Associated with Olefin Functionalization



Scheme 3. Synthesis of Tetrasubstituted Olefin via Ireland−Claisen Rearrangement[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMAP, CH_2Cl_2, r.t., 73%; (b) isopropenylmagnesium bromide (**14**), $LaCl_3$·2LiCl, THF, then **13**, 0 °C to r.t., 86%, *dr* = 6:5; (c) $PhNMe_2$, AcCl, 50 °C, 64%; (d) LiHMDS, TBSCl, HMPA, THF, −78 °C to r.t., then 1 M HCl; (e) MeI, K_2CO_3, DMF, r.t., 87% over two steps, *dr* = 2.3:1; (f) DIBAL-H, PhMe, −78 °C to r.t., 59% *trans*-**17**, 27% *cis*-**17**.

Transition-metal-catalyzed semireductions of dienes by Cr and Ru catalysts have been reported to proceed via the *s-cis* η^4 complex/metallacyclopentene, delivering single olefin isomers (Scheme 4).[13] The configuration of the tetrasubstituted olefin would be controlled by the structure of the coupling partners and the reduction mechanism. While the first reports on diene semihydrogenation date back to the 1960s, there is only one report, by Shibasaki, for the synthesis of a tetrasubstituted olefin (trialkyl-substituted acrylonitrile) in a complex structure via semihydrogenation of a 1,3-diene.[13b] This report predates coupling chemistry, and numerous steps were required to access the 1,3-diene. The combination of modern sp^2−sp^2 cross-coupling reactions and 1,4-semihydrogenation would allow for rapid access to a tetrasubstituted olefin in a stereodefined manner (Scheme 4).

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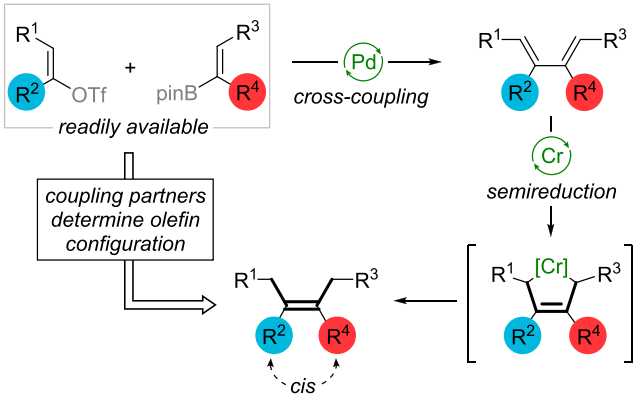
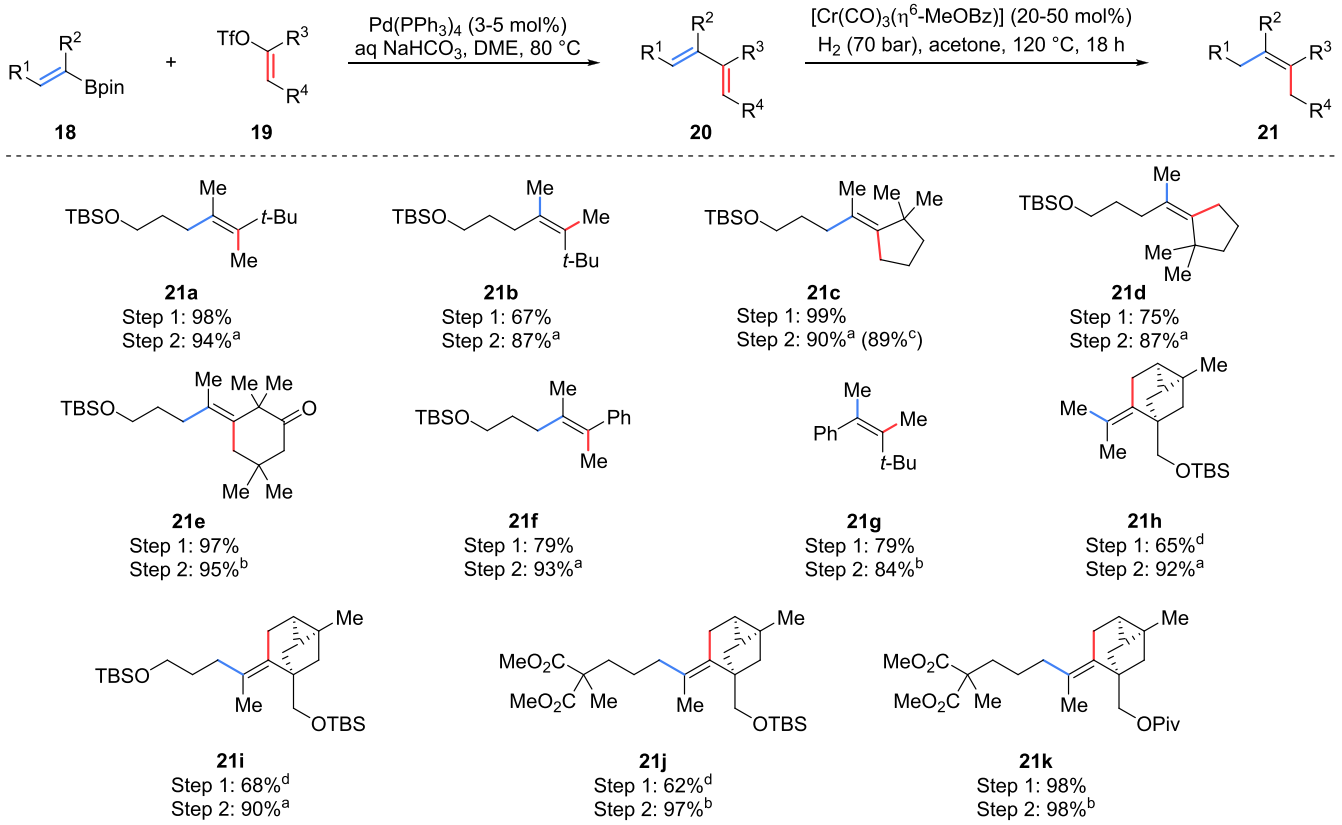
Scheme 4. Conceptual Approach to Tetrasubstituted Olefin Synthesis via Cross-Coupling and 1,4-Semihydrogenation



To study this approach, we prepared a series of dienes **20** via Suzuki cross-coupling[14] of vinyl boronates **18** with vinyl triflates **19** and subjected them to semihydrogenation conditions (Table 1).[15] We selected [$Cr(CO)_3(\eta^6$-MeOBz)] as the catalyst for the 1,4-semihydrogenation over Cp*Ru-based catalysts as very high yields and stereoselectivities have been reported for the application of this catalyst and it is readily accessible in one step from commercially available $Cr(CO)_6$ and MeOBz.[13d] We focused on tetrasubstituted olefins featuring the same stereochemical challenges as encountered in the natural product. As the design of the cross-coupling partners determines the olefin geometry, varying the coupling partners allows for the selective preparation of both olefin isomers. Accordingly, both olefin isomers **21a** and **21b** as well as **21c** and **21d** could be prepared in high stereoselectivities and yields from the corresponding vinyl triflates and boronates. For **21c** and **21d**, the olefin geometries were confirmed by 2D NOESY NMR experiments (see SI for details). The ketone in **21e** was well tolerated under cross-coupling and hydrogenation conditions (97% and 95% yield, respectively). Also, styrenes **21f** and **21g** could be prepared selectively. Next, we turned our attention to the synthesis of tetrasubstituted olefins on the tricyclo[3.2.1.$0^{2,7}$]-octane scaffold. In a first attempt, a symmetric isopropylidene substituent could be installed successfully (**21h**). During the cross-coupling reaction, most of the silyl ether was cleaved and the alcohol was reprotected prior to hydrogenation. Employing more complex vinyl boronates, **21i** and **21j** were synthesized stereoselectively. Changing the protecting group to pivalate was well tolerated under both cross-coupling and hydrogenation conditions, and **21k** was obtained in 96% over two steps. All hydrogenation reactions were initially performed using 20 mol% catalyst. This led to incomplete conversion for **21e**, **21g**, **21j**, and **21k**. Increasing the catalyst loading to 50 mol% ensured full conversion for these substrates. All tetrasubstituted olefins **21** were obtained in >20:1 *dr*. In most cases, only traces of regioisomeric olefins (<5%) were observed. For **21c**, decreasing the catalyst loading to 5 mol% led to 54% conversion after 18 h. After the reaction time was increased to 42 h, full conversion and 89% yield was observed showing that the catalyst is still active after the standard

Table 1. Synthesis of Tetrasubstituted Olefins via Cross-Coupling and Semihydrogenation



[a]20 mol% catalyst was used. [b]50 mol% catalyst was used. [c]5 mol% catalyst was used for 42 h. [d]During the cross-coupling, most of the silyl ether was cleaved and was reformed using TBSCl, imidazole and DMAP (10−20 mol%) in CH_2Cl_2 at r.t. The yields refer to combined yields over two steps.

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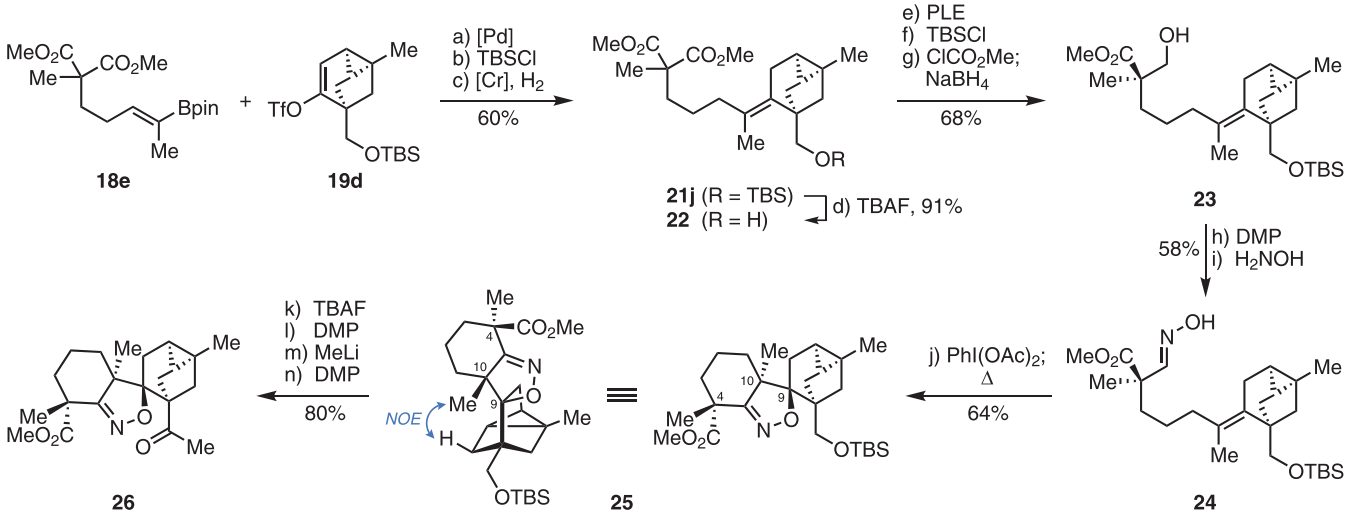
Scheme 5. Synthesis of Isoxazoline 26 via Nitrile Oxide Cycloaddition[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (3 mol%), $NaHCO_3$, DME−H_2O (9:1), 80 °C, then HCl, MeOH, r.t., 66%; (b) TBSCl, imidazole, DMAP (20 mol%), CH_2Cl_2, r.t., 94%; (c) H_2 (70 bar), [$Cr(CO)_3(\eta^6$-MeOBz)] (50 mol%), acetone, 120 °C, 97%; (d) TBAF, THF, r.t., 91%; (e) pig liver esterase (PLE), aq NaOH, 0.1 M pH 7 sodium phosphate buffer−DMSO (10:1), r.t., *dr* = 20:1; (f) TBSCl, imidazole, DMAP, CH_2Cl_2, r.t.; K_2CO_3, MeOH−THF−H_2O (20:10:3), r.t.; (g) $ClCO_2Me$, Et_3N, THF, 0 °C to r.t.; $NaBH_4$, MeOH, 0 °C, 68% over three steps; (h) DMP, *t*-BuOH, CH_2Cl_2, r.t., 71%; (i) H_2NOH·HCl, EtOH−pyr (8:1), r.t., 82%; (j) $PhI(OAc)_2$, MeOH, 0 °C; PhMe, Δ, 64%; (k) TBAF, THF, 60 °C, 99%; (l) DMP, *t*-BuOH, CH_2Cl_2, r.t., 86%; (m) MeLi, THF−Et_2O (3:1), −78 °C; (n) DMP, *t*-BuOH, CH_2Cl_2, r.t., 94% over two steps.

reaction time. Decreasing the H_2 pressure to 55 bar completely shut down the reaction. Notably, variation of the concentration between 7 and 50 mM and scaling-up the reaction to 2.3 mmol for **21j** had no effect on yield or stereoselectivity.

We continued our efforts toward the synthesis of (−)-mitrephorone A (**1**) using **21j**, which was prepared from vinyl boronate **18e** and vinyl triflate **19d** (Scheme 5). For malonate desymmetrization, we turned to the application of biocatalysis for the stereoselective monohydrolysis of α,α-disubstituted malonate **21j**. Subjecting malonate **21j** to pig liver esterase (PLE) in a mixture of aqueous phosphate buffer and DMSO (10:1) did not lead to any conversion of starting material.[16] In contrast, after silyl ether cleavage with TBAF, the corresponding malonic acid monoester was obtained in 20:1 *dr* under the same reaction conditions. Reprotection of the hydroxy group with TBSCl and chemoselective reduction of the carboxylic acid to the corresponding alcohol ($ClCO_2Me$ followed by $NaBH_4$) afforded alcohol **23** in 68% from malonate **22**.[17] Oxime **24** was obtained via oxidation with DMP and treatment with hydroxylamine hydrochloride in 58% yield over two steps. Subjecting **24** to $PhI(OAc)_2$ led to its oxidation to the corresponding nitrile oxide,[18] which underwent cycloaddition to give isoxazoline **25** in 64% yield as a single diastereomer as determined by analysis of the ^{1}H NMR spectrum. The relative configuration was established by 1D NOE NMR experiments (see SI for details). It is worth noting that the cycloaddition sets two challenging stereocenters, namely the vicinal tertiary ether and quaternary center concomitant with 6-membered ring formation. Notably, when a 1:1 mixture of diastereomers of oxime **24** (epimeric at C_4) was subjected to the reaction conditions, two diastereomers were obtained that have the same relative configuration at C_4, C_9, and C_{10} as determined by X-ray crystallography (see SI for details). This clearly shows that the facial selectivity in the dipolar cycloaddition is fully controlled by the α stereocenter of the nitrile oxide.

Examination of putative transition states as shown for **I** and **II** in Figure 1 proves instructive. Transition state **I**,

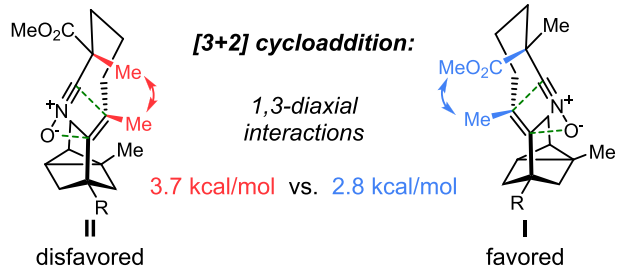


Figure 1. Putative transition states for nitrile oxide cycloaddition.

incorporating a 1,3-diaxial interaction between an ester and a methyl group, is energetically favored over transition state **II**, in which a 1,3-dimethyl axial interaction is present (~2.8 vs ~3.7 kcal/mol).[19] This is consistent with the formation of a single diastereomer as observed by ^{1}H NMR spectroscopy.

A common problem in nitrile oxide cycloaddition is dimerization of the nirile oxide, and it has been shown that cycloreversion can be induced by heating.[20] However, we did not observe any dimer, and all byproducts were highly polar baseline compounds, which could not be characterized.

Despite being scalable and relatively high yielding (7.6% over 16 steps from **12**), we aimed to further optimize the route toward isoxazoline **26** with respect to the following points: (1) Achiral vinyl boronate **18e** could be replaced by a chiral, enantioenriched analogue **27**, which would render the synthesis more convergent (Scheme 6). It is important to note that the *dr* of coupling product **28** will depend on the *ee* of vinyl boronate **27**. (2) The protecting group strategy is suboptimal: The TBS ether in vinyl triflate **19d** is cleaved during cross-coupling and was reprotected for hydrogenation but enzymatic desymmetrization only proceeded with the free alcohol. So again a sequence of deprotection, desymmetrization, and reprotection had to be carried out. Transformation of the alcohol to the corresponding methyl ketone prior to cross-coupling may improve the synthesis.

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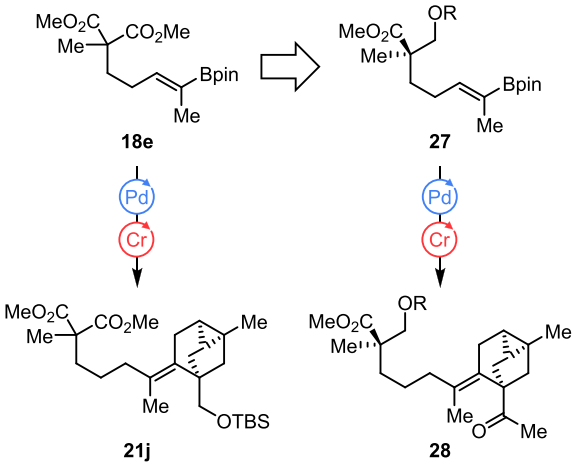
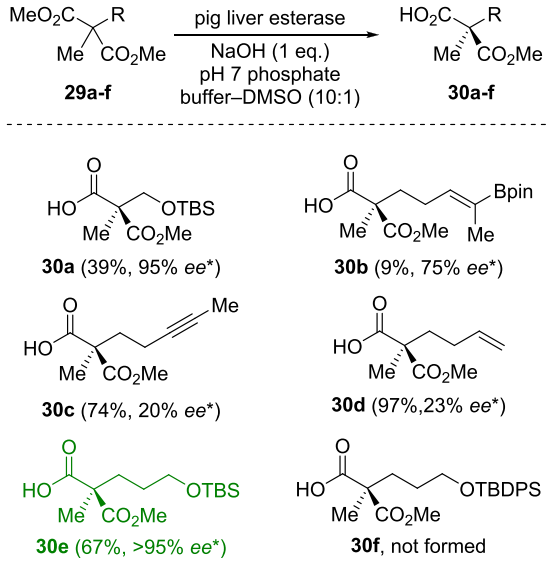
Scheme 6. Envisioned Optimization of the Route



Malonate Desymmetrization Studies. For the asymmetric synthesis of enantioenriched vinyl boronate **27**, we wanted to further explore the stereoselective monohydrolysis of α,α-disubstituted malonates. Previous studies on desymmetrization of 2-methyl-2-alkylmalonates **29** have shown that the length of R has a strong effect on the enantioselectivity in the hydrolysis to give **30**.[21] Accordingly, we prepared a series of malonates **29a–f**, which vary in length and nature of side chain and, after enzymatic transformation, could all be elaborated to **7** (Table 2).[22,23] Dimethyl malonates **29** may be conveniently prepared by alkylation reactions.[24] For rapid determination of enantioselectivities in our study, we developed a quick assay involving coupling of acids **30** with (*S*)-phenylethanamine to the corresponding diastereomeric amides.[25] To benchmark the method, we repeated the pig liver esterase-mediated hydrolysis of TBS-protected 2-methyl-2-hydroxymethylmalonate **29a**, which has been previously reported by Keese.[16] The enantiomeric excess we observed for the formation of **30a** was in full agreement with Keese's result (95% *ee*). When we subjected vinyl boronate **29b** to the enzymatic step, low yield (9%) and modest enantioselectivity (75% *ee*) were observed. Consequently, we examined the enzymatic reaction with **29c** and **29d**, which furnished products in 74% and 97% yield, respectively, albeit in low enantiomeric excess, 20% and 23% *ee*, respectively. Examination of silyl ethers **29e** and **29f** revealed that the former afforded **30e** in 67% yield and the highest enantiomeric excess, namely >95% *ee*. Interestingly, no reaction was observed for the analogous TBDPS-protected substrate **29f**.[26] As a consequence of its high yield and enantiomeric excess, **30e** was selected for further studies. Based on previous investigations, the absolute configuration of carboxylic acid **30e** was tentatively assigned as (*R*).[16,21]

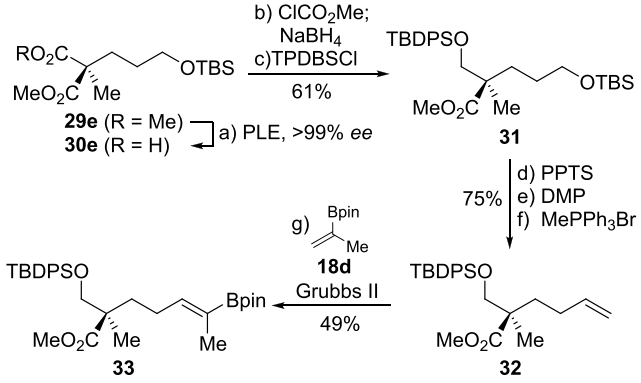
Table 2. Enzymatic Desymmetrization of Malonates 29[a]



[a]Enantiomeric excesses (*ee*) were determined by analysis of the ^{1}H NMR spectra after amide coupling with enantiopure (*S*)-phenylethanamine, see SI for details.[25]

Synthesis of Vinyl Boronate 33. Enantiopure[27,28] malonic acid monoester **30e** was transformed into silyl ether **31** via chemoselective reduction of the carboxylic acid to the corresponding alcohol ($ClCO_2Me$ followed by $NaBH_4$),[17] and TBDPS protection in 61% yield from **29e** (Scheme 7).

Scheme 7. Synthesis of Vinyl Boronate 33[a]



[a]Reagents and conditions: (a) pig liver esterase (PLE), aq NaOH, 0.1 M pH 7 sodium phosphate buffer–DMSO (10:1), r.t.; (b) $ClCO_2Me$, Et_3N, THF, 0 °C to r.t.; $NaBH_4$, MeOH, 0 °C, 64% from **29e**; (c) TBDPSCl, imidazole, DMAP (20 mol%), CH_2Cl_2, r.t., 95%; (d) PPTS (20 mol%), EtOH, r.t.; (e) DMP, *t*-BuOH, CH_2Cl_2, r.t., 87% over two steps; (f) $MePPh_3Br$, KO*t*-Bu, THF, r.t., 86%; (g) isopropenylboronic acid pinacol ester (**18d**), Grubbs second-generation catalyst (10 mol%), CH_2Cl_2, 50 °C, 49%.

Selective cleavage of the TBS-ether in **31** with PPTS in ethanol,[29] subsequent oxidation with DMP, and Wittig methylenation of the resulting aldehyde afforded olefin **32** in 75% yield over three steps. Vinyl boronate **33** was prepared via cross-metathesis of **32** with isopropenylboronic acid pinacol ester (**18d**) in 49% yield.[23]

Synthesis of Tetrasubstituted Olefin 37. We subsequently transformed hydroxyketone **12**[7] into a suitable building block for cross coupling. Following a short sequence (Comins reagent (**34**); DMP; MeLi; DMP), **35** was prepared (Scheme 8).[30] Cross-coupling of **35** with vinyl boronate **33** afforded 1,3-diene **36** in 65% yield.[14] Intermediate **36** was subjected to hydrogenation conditions in the presence of 50 mol% of catalyst [$Cr(CO)_3(\eta^6$-MeOBz)]. Desired tetrasubstituted olefin **37** was obtained in 93% yield as a single olefin isomer.

Completion of the Carbon Skeleton via Nitrile Oxide Cycloaddition. Silyl ether **37** was converted into oxime **38** via deprotection with TBAF, oxidation with DMP and oxime

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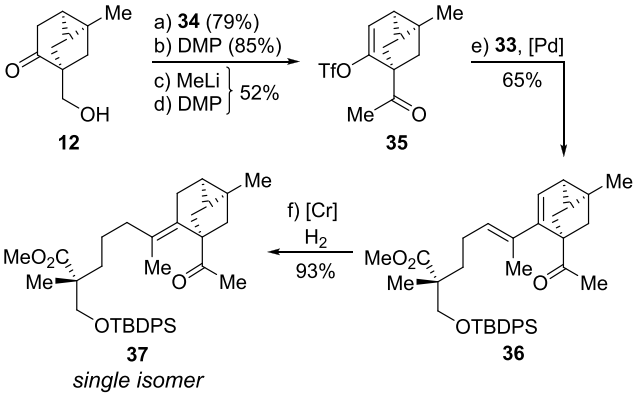
Scheme 8. Synthesis of Tetrasubstituted Olefin 37[a]

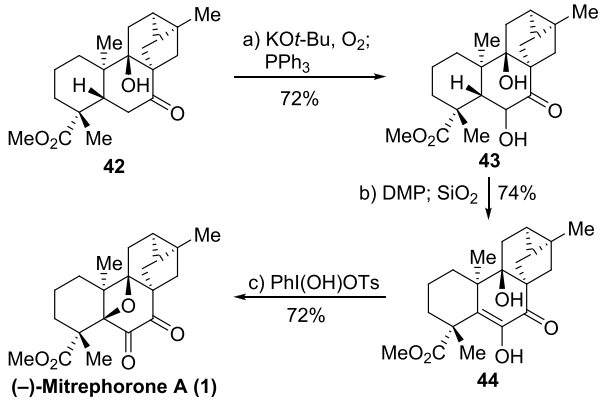


[a]Reagents and conditions: (a) TMSCl, imidazole, THF, r.t., then KHMDS, −78 °C, then Comins reagent (**34**), −78 °C, then aq HCl, r.t., 79%; (b) DMP, *t*-BuOH, CH_2Cl_2, r.t., 85%; (c) MeLi, THF, −78 °C; (d) DMP, *t*-BuOH, CH_2Cl_2, r.t., 52% over two steps; (e) **33**, $Pd(PPh_3)_4$ (2.5 mol%), $NaHCO_3$, DME−H_2O (9:1), 85 °C, 65%; (f) H_2 (70 bar), [$Cr(CO)_3(\eta^6$-MeOBz)] (50 mol%), acetone, 120 °C, 93%.

formation with hydroxylamine hydrochloride in 62% yield over three steps (Scheme 9).[6c] Subjecting **38** to the same nitrile oxide cycloaddition conditions as described above afforded isooxazoline **26** in 52% yield as a single diastereomer along with 10% recovered starting material. No side products were observed in significant quantities (>5% yield). Enolization of **26** with LDA or synthesis of the corresponding trimethylsilyl enol ether followed by treatment with $BF_3{\cdot}OEt_2$ did not induce intramolecular addition to the isoxazoline. In contrast, after *N*-methylation of **26** using Meerwein's salt (Me_3OBF_4),[31] the intermediate isoxazolinium salt **39** was subjected in situ to TMSOTf and Et_3N to induce cyclization. The Mannich-type reaction afforded isoxazolidine **40** in 69% yield and completed the carbon skeleton of the natural product. Treatment of **40** with Zn in AcOH at 50 °C led to N−O bond cleavage with concomitant methylamine elimination to give enone **41** in 65% yield. Various attempts to induce oxa-Michael addition of **41** and either trapping the resulting enolate as the corresponding enol ether (e.g., TBSOTf, 2,6-lutidine or proton sponge) or oxidizing it (IPh_2BF_4, $I_2/NaHCO_3$, NBS/$NaHCO_3$, $PhI(OAc)_2$/KO*t*-Bu, O_2/KO*t*-Bu, MoOPH/KHMDS) were unsuccessful. Also, oxidative transformation of the enone to the diosphenol proved unfruitful (epoxidation followed by rearrangement or dihydroxylation followed by elimination). At this point, **41** was reduced to the corresponding saturated ketone **42** with H_2 and Pd/C in 77% yield.[32] Isoxazolidine **40** could also be directly reduced to **42** using H_2 and Pd/C in the presence of AcOH at 80 °C in 72% yield.

α-Oxidation of **42** (O_2, KO*t*-Bu, then PPh_3) gave *α*-hydroxyketone **43** in 72% yield (Scheme 10).[33] Treatment

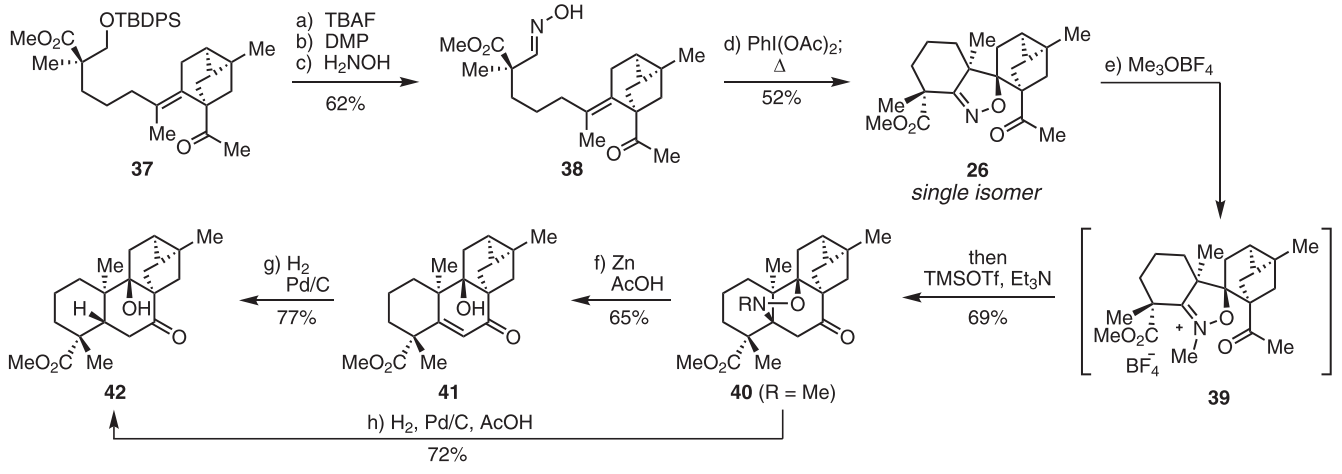
Scheme 10. Completion of the Synthesis[a]



[a]Reagents and conditions: (a) KO*t*-Bu, O_2, THF, −78 °C, then PPh_3, −78 °C to r.t., 72%; (b) DMP, *t*-BuOH, CH_2Cl_2; SiO_2, hexane−EtOAc (3:1), 74%; (c) PhI(OH)OTs, $NaHCO_3$, CH_2Cl_2, 72%.

with DMP furnished hydroxydiosphenol **44** in 74% yield. It is worth noting that oxidation of **42** to diosphenol **44** was carried out in an efficient sequence with the tertiary alcohol being unprotected. This was not possible in our first route employing an isomeric ketone, which necessitated protection of the tertiary alcohol as its silyl ether.[3] Finally, (−)-mitrephorone A (**1**) was obtained via oxidative cyclization of **44** mediated by

Scheme 9. Synthesis of 42 via Nitrile Oxide Cycloaddition[a]



[a]Reagents and conditions: (a) TBAF, THF, r.t.; (b) DMP, *t*-BuOH, CH_2Cl_2, r.t., 73% over two steps; (c) $H_2NOH{\cdot}HCl$, pyr−EtOH (8:1), r.t., 85%; (d) $PhI(OAc)_2$, MeOH, 0 °C; PhMe, Δ, 52%; (e) Me_3OBF_4, CH_2Cl_2, r.t., then TMSOTf, Et_3N, r.t., 69%; (f) Zn, AcOH, 50 °C, 65%; (g) H_2 (1 atm), Pd/C (30 mol%), EtOAc, r.t., 77%; (h) H_2 (1 atm), Pd/C, EtOAc−AcOH (5:1), 80 °C, 72%.

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Koser's reagent (PhI(OH)OTs) in the presence of $NaHCO_3$ in 72% yield and >99% *ee*, which compares favorably with previous total syntheses (88 and 85% *ee*).[3,4a,34,35] Spectroscopic data of the material we obtained is identical with that reported for the natural isolate.[2]

CONCLUSION

We have reported a highly enantioselective and diastereoselective total synthesis of (−)-mitrephorone A (**1**, >99% *ee*). The synthesis relies on intramolecular nitrile oxide cycloaddition, which sets two stereocenters, forms one all-carbon ring and introduces an isoxazoline, which serves as a handle for elaboration of the cycloadduct to the natural product. Additional salient features of the synthesis include highly enantioselective pig liver esterase-catalyzed malonate desymmetrization, 1,4-semihydrogenation of a 1,3-diene, and hypervalent iodine-mediated oxidative cyclization to furnish the oxetane. Stereo- and regioselective synthesis of tetrasubstituted double bonds via sp^2−sp^2 cross-coupling and 1,4-semihydrogenation has no precedence and represents a powerful method for olefin synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09520.

Experimental procedures and characterization data for all new compounds (PDF)

Crystallographic data for a mixture of **25** and its diastereomer **S6** (CIF)

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Notes

The authors declare no competing financial interest.

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(26) None of the investigated malonates **29** is well soluble in the phosphate buffer. The absence of reactivity for **29f** may be attributed to (1) lack of solubility or (2) poor fit into the enzyme pocket. The aqueous conditions required for the enzymatic resolution along with accessibility to the lipase active site result in dependences on substrate structure that are subtle.
(27) The assay used for determination of enantiomeric excesses in Table 2 has its limitations for *ee*'s > 90% because the *dr*'s of the ester amides cannot be accurately determined by ^{1}H NMR analysis. Therefore, carboxylic acid **30e** was reduced to the corresponding alcohol followed by benzoylation. The enantiomeric excess was determined by chiral HPLC (>99% *ee*, see SI for details).
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