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Total Synthesis of (–)-Mitrephorone A

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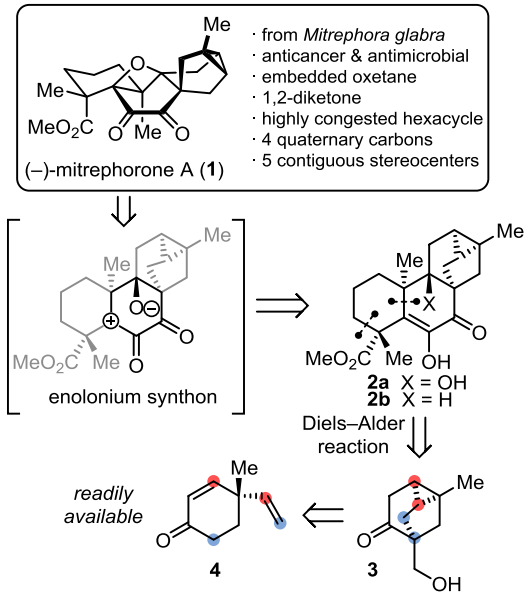
ABSTRACT: The first synthesis of (–)-mitrephorone A is disclosed along with discussion and study of synthetic strategies. The natural product includes a highly congested hexacyclic *ent*-trachylobane diterpenoid framework featuring a rare, embedded oxetane. The synthetic analysis presented dissects a number of approaches for the synthesis of the central oxetane, including carbonyl-olefin photocycloadditions, Prins-type cyclizations, and oxidative ring closures. In the successful route, three [4+2] cycloadditions enable rapid construction of all carbocycles. A novel late-stage oxidative cyclization of a hydroxy diosphenol with Koser's reagent furnishes the pivotal oxetane moiety.

Introduction

The anticancer agent taxol is the most notable example of oxetane-containing natural products.[1] Although in synthetic endeavors to taxol accessing the oxetane is tangential,[2] there are numerous other targets, wherein installation of the oxacycle is central to the synthesis strategy. These include thromboxane A_2,[3] oxetanocin A,[4] oxetin,[5] merrilactone A,[6] and more recently dictyoxetane.[7] Isolated in 2005 by Oberlies and co-workers from the Bornean shrub *Mitrephora glabra*, (–)-mitrephorone A (**1**) contains a fully substituted oxetane embedded in a pentacyclic carbon skeleton (Scheme 1).[8] The pentacyclic carbon skeleton and tricyclo[3.2.1.$0^{2,7}$]octane scaffold render (–)-mitrephorone A a member of the family of *ent*-trachylobanes.[9] In addition to antimicrobial activity, this diterpene exerts potent and broad cytotoxicity against various cancer cell lines (MCF-7, NCI-H460, SF-268), which has been largely attributed to the oxetane. In this respect, (–)-mitrephorone B (**2b**) displays no activity when examined in the same assay.[8]

Scheme 1. Structure/Activity of (–)-Mitrephorone A and Retrosynthetic Analysis



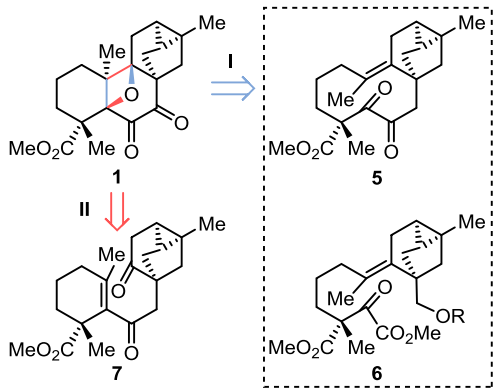
The highly congested structure features a tetrasubstituted cyclopropane, four quaternary centers and five contiguous stereocenters. Additionally, the presence of a rare 1,2-diketone render this natural product a veritable challenge in synthetic chemistry. Herein, we report the first and enantioselective total synthesis of (–)-mitrephorone A along with accompanying synthetic studies. The salient features of the strategy include cycloaddition reactions to gain rapid entry to the carbocyclic framework along with oxidative cyclization of a hydroxy enol ketone to afford the central oxetane.

Results and Discussion

Retrosynthetic Analysis. The key challenge presented by (–)-mitrephorone A is the unusual hexasubstituted oxetane, including a stereogenic quaternary center, fully integrated in the diterpene scaffold. Accordingly, at the heart of the retrosynthetic analysis are the oxetane and the means for its introduction. The fully substituted oxacycle precludes consideration of alkylative ring-closing strategies at tertiary C(sp^3) centers, which are expected to be challenging. A strategy involving intramolecular, carbonyl-olefin [2+2] cycloaddition might overcome this limitation as Paternò–Büchi reactions have proven successful for highly substituted substrates.[10] Concerted formation of the apposite C–O and C–C bonds enables two disconnection strategies **I** and **II** (Scheme 2).

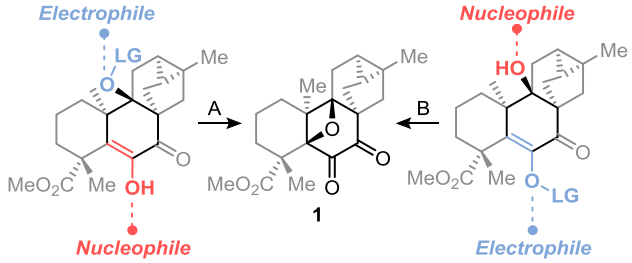
In strategy **I** (bond disconnection in blue) there are two options. In the first of these, the decalyl system is produced by transannular cycloaddition reaction. Because the starting *trans*-cyclodecene in **5** can exist in at least two atropodiastereomeric forms, the system is considerably complicated, especially when contrasted against the second alternative. In this regard, α-ketoester **6** lacks a macrocycle, is easier to prepare, and the β-stereocenter may provide a bias for stereocontrol in a Paternò–Büchi reaction. In strategy **II** (bond disconnection in red), formation of the oxetane would result from intramolecular [2+2] cycloaddition of enone **7**. An attractive feature of this approach is that **7** may be retrosynthetically partitioned into two similarly-sized fragments.

Scheme 2. Strategic Disconnection of the Oxetane Core Employing a [2+2] Cycloaddition Approach



In an altogether different analysis, the juxtaposition of the oxetane and α-diketone in **1** suggests an approach involving an enolonium C(sp^2) synthon (Scheme 1). Two mechanistically distinct approaches can be considered for oxetane construction in (–)-mitrephorone A (Scheme 3). In one of these, the nucleophilic enol or enolate attacks an electrophilic oxygen, such as a hydroperoxide (LG = OH, pathway A). In this context, Dussault and co-workers had demonstrated that γ-peroxyketones are readily transformed into ketooxetanes under basic conditions.[11]

Scheme 3. Complementary Modes of Oxidative Cyclization

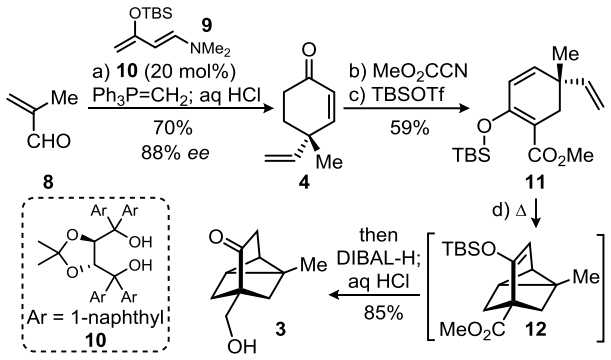


In another approach, the enone functions as an electrophile that is engaged by the nucleophilic tertiary alcohol, forming the oxetane as part of an oxidative cyclization (pathway B). Experimentally, the latter is a more flexible approach given the variety of options available for the identity of the leaving group (LG), which includes metals, halides and sulfonates, among others.[12] There are but four examples reported in the literature in which α'-hydroxy methyl ketones are converted into oxetanyl ketones by treatment with PhI(OAc)$_2$;[12b] the reaction appears to only work in 70-75% yield for closely related 17β-acetyl-17α-hydroxysteroids. However, the reaction of the simpler substrate1-acetyl-1-hydroxycyclohexane was reported to proceed in about 10% yield. To the best of our knowledge, there is no precedence for hydroxy diosphenol substrates oxidatively closing to the corresponding oxetanyl diketones. This second approach with the enone as acceptor can be considered synthetically equivalent to the process invoking an enolonium synthon.

The ester attached to the decalyl fragment of **2a** (Scheme 1) alludes to the implementation of an intramolecular Diels–Alder reaction to furnish both rings in a single step.[13] This approach prescribes the use of a tricyclo[3.2.1.0^{2,7}]octane (**3**) as a starting point. Cursory examination of **3** would suggest cyclopropanation approaches for its synthesis. However, closer inspection revealed that **3** might be derived from intramolecular cycloaddition of a 5-vinyl-1,3-cyclohexadiene derivative of **4**, joining C(●)-C(●) and C(●)-C(●). First reported in 1968,[14a] this type of Diels–Alder reaction that leads to a cyclopropane has been the subject of methodological studies,[14b-n] but to the best of our knowledge this powerful transformation has not been utilized in the context of a total synthesis.

[2+2] Cycloaddition Studies. The synthesis of **1** commenced with TADDOL-catalyzed Diels–Alder reaction of methacrolein (**8**) with Rawal's diene (**9**),[15] followed by Wittig methenylation and acidic hydrolysis[16] to afford cyclohexenone **4** in 70% overall yield and 88% *ee* (Scheme 4). Introduction of a methyl ester using Mander's reagent[17] and TBS protection gave triene **11** in 59% overall yield. This efficient sequence set the stage for intramolecular cycloaddition to generate the cyclopropane. Thus, heating a solution of **11** in toluene at 190 °C gave **12** as a single product. The addition of propylene oxide as acid scavenger to the reaction mixture proved vital to prevent hydrolysis of the starting material over the course of the reaction.[18] Subsequent *in situ* reduction of the ester with DIBAL-H and quenching with aqueous HCl yielded hydroxyketone **3** (85%).

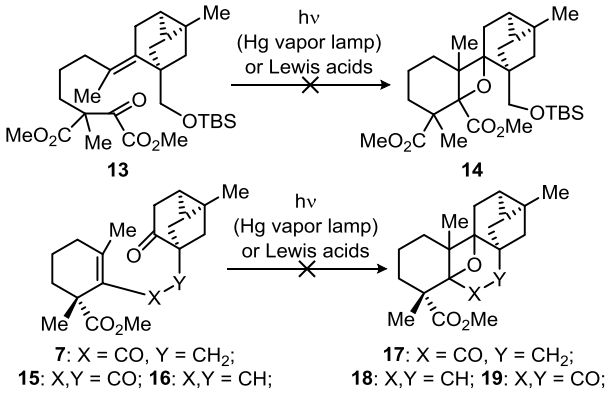
Scheme 4. Construction of the Tricyclooctane Core[a]



[a]Reagents and conditions: (a) Rawal's diene (**9**), (*S*,*S*)-1-Np-TADDOL (**10**) (20 mol%), PhMe, –80 °C, then $Ph_3P{=}CH_2$, –78 °C to RT, then 1 M aq HCl, RT, 70%, 88% *ee*; (b) LDA, THF, –78 °C, then HMPA, MeO_2CCN; (c) LiHMDS, *t*-$BuMe_2SiOTf$, THF, –78 °C, 59% (2 steps); (d) propylene oxide, PhMe, 190 °C, then DIBAL-H, –78 °C, then 1 M aq HCl, –78 °C to RT, 85%.

Having established a reliable and scalable route to **3**, precursors to probe both [2+2] strategies (Scheme 2) were rapidly accessed (see SI). However, extensive studies on either

Scheme 5. Investigation of [2+2] Cycloadditions

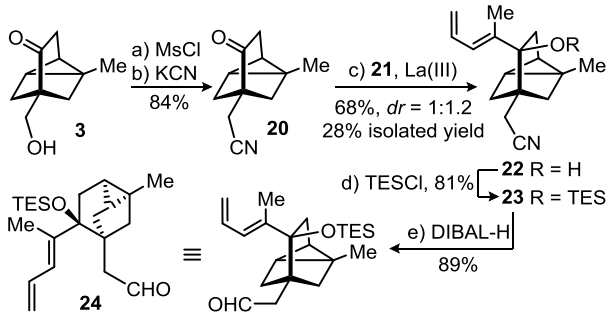


system were not met with success (Scheme 5). For example, irradiation of a solution of ketoester **13** in deuterated benzene in a quartz vessel with a 400 W mercury-vapor lamp at RT gave Norrish type II products along with decomposed material. Irradiation of ketones **7**, **15**, and **16** in various solvents (PhH, MeCN, $CDCl_3$) resulted in recovery of the starting material or gave complex mixtures. Isomerization of the 1,2-disubstituted cis-olefin in **16** to the trans isomer was also observed.

We proceeded to examine oxetane formation from carbonyl olefins mediated by acids.[19] Common reagents such as $TiCl_4$, $BF_3{\cdot}OEt_2$, Me_2AlCl and other aluminum based Lewis acids routinely afforded unreacted starting material or complex mixtures. Neither oxetane products nor Prins-type intermediates were observed. Presumably, the sterically demanding environment at the carbonyl group hampered nucleophilic attack by the olefin. We also examined Brønsted acids to promote cyclization. For instance, treatment of **7** with anhydrous HCl in 1,4-dioxane returned starting material, even at elevated temperatures (70 °C). Addition of triflic acid at 0 °C to a solution of **7** in CH_2Cl_2 gave a complex mixture. In light of these unsuccessful approaches, we turned our attention to the oxidative cyclization strategy.

Towards the Diels–Alder Reaction. Construction of the remaining two carbocycles was addressed. Conversion of the primary alcohol in **3** to the homologated aldehyde provides a handle for the introduction of various dienophiles. *O*-Mesylation followed by treatment with KCN in hot DMSO gave neopentylic nitrile **20** in 84% yield (Scheme 6).[20]

Scheme 6. Elaboration of the Tricyclooctane Core[a]

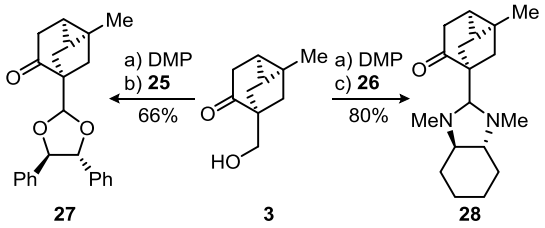


[a]Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C; (b) KCN, DMSO, 80 °C, 84% (2 steps); (c) (*E*)-tributyl(penta-2,4-dien-2-yl)stannane, *n*-BuLi (penta-2,4-dien-2-yllithium (**21**)), THF, –78 °C, then **20**, $LaCl_3{\cdot}2LiCl$, THF, –78 °C, 68% (*dr* = 1:1.2); (d) Et_3SiCl, imidazole, DMF, 80 °C, 81%; (e) DIBAL-H, PhMe, –78 to 0 °C, 89%.

We then examined introduction of the 1,3-diene for the targeted Diels–Alder cycloaddition reaction. However, ketone **20** proved inert towards addition by dienyllithium **21**, presumably as a consequence of competitive enolization. Knochel and coworkers have reported the use of soluble lanthanum salts to enable addition of Grignard reagents to sterically hindered ketones.[21] In our hands, ketone **20** reacted with dienyllithium **21** in the presence of $LaCl_3{\cdot}2LiCl$ to furnish tertiary alcohol as a separable mixture of diastereomers (68%, dr = 1:1.2), from which **22** was isolated in 28% yield. Structural analysis of ketonitrile **20** revealed that the methyl group, which breaks the mirror symmetry of the carbon framework, is considerably distanced to the carbonyl group, and thus it imposes low stereoinduction on the nucleophilic addition. Extensive investigations were undertaken to improve the diastereoselectivity in the ketone addition reaction. An overview of the various approaches is provided in Table 1 (see SI for detailed experimental studies).

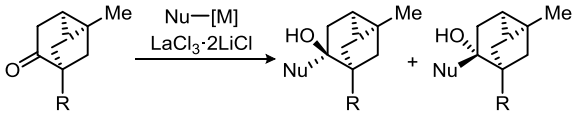
In order to optimize facial selectivity in the ketone addition reaction, three different approaches were investigated: 1) use of chiral auxiliaries, 2) addition of chiral ligands for RLi/La or R_xZn and 3) variation of reaction conditions. We reasoned that maximum effect of a chiral auxiliary would be observed by its installation in close proximity to the ketone. In this respect, oxidation of the primary alcohol in **3** offers the opportunity to introduce a chiral acetal[22] or aminal.[23] Dess–Martin oxidation of hydroxyketone **3** to the corresponding aldehyde followed by condensation with either (*R*,*R*)-hydrobenzoin (**25**) or (*R*,*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**26**) gave acetal **27** and aminal **28**, respectively (Scheme 7).

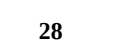
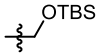
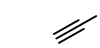
Scheme 7. Synthesis of Acetal 27 and Aminal 28[a]



[a]Reagents and conditions: (a) Dess–Martin periodinane (DMP), *t*-BuOH, CH_2Cl_2, RT; (b) (*R*,*R*)-hydrobenzoin (**25**), *p*-TsOH·H_2O (10 mol%), PhMe, 50 °C, 66% (from **3**); (c) (*R*,*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**26**), PhH, 70 °C, 80% (from **3**).

Table 1. Studies of Addition to Various Ketones



entry	substrate	conditions	dr
1	**27**	**21**, THF, 0 °C to RT	1:1.2[a]
2	**28**	**21**, THF, –45 °C to RT	–[b]
3		 , THF, 0 °C to RT	6:1[a,c]
4	 **29**	 , $ZnMe_2$, (*S*,*S*)-salen, PhMe, RT	–[b]
5	**3**	**21**, (+)-sparteine, THF, –45 to –20 °C	1:1.2[a]
6		**21**, THF–Et_3N (1:1)	1:1.2[a]
7		**21**, THF–TMEDA (4:3)	1:1.2[a]

[a]Determined by ^1H NMR analysis of the crude mixture. [b]No conversion of the starting material. [c]The diastereomers were not assigned.

Addition of dienyllithium **21** to **27** (entry 1) resulted in the same diastereoselectivity as observed for the addition to **20** (dr

= 1:1.2). Under the same reaction conditions, aminal **28** (entry 2) did not furnish adduct. The use of other transmetalation protocols or dienylmetal species (Mg, Ce) also led to full recovery of the starting material. In contrast, isopropenylmagnesium bromide added cleanly to ketone **28** (entry 3) and gave the corresponding tertiary alcohol as a mixture of diastereomers in a ratio of 6:1 as determined by ^{1}H NMR analysis of the unpurified product. Despite the improved selectivity, conversion of the 1,1-disubstituted olefin to diene **24** would require multiple steps, reducing the efficiency of the route.

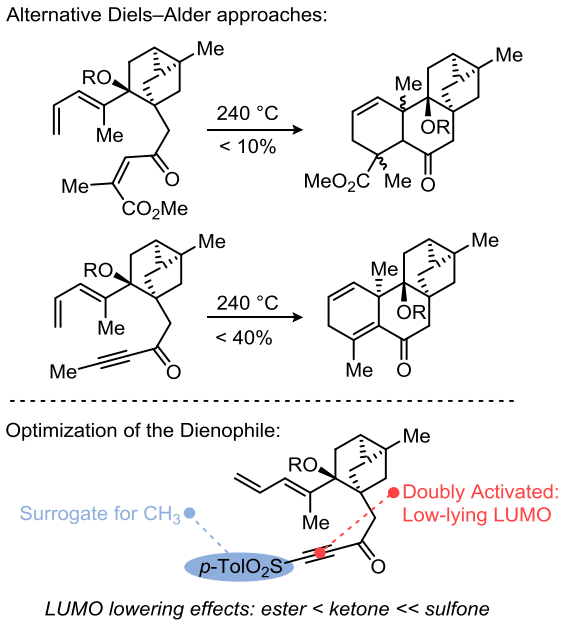
A broader study on stereoselective additions to ketones **3** and **29** was undertaken that included examination of the influence of chiral ligands/additives. Cozzi has documented stereoselective alkynylation of hindered, enolizable ketones employing (*S*,*S*)-salen-Zn complexes to give tertiary alcohols in up to 81% ee.[24] Unfortunately, under similar conditions, starting material **29** was recovered unchanged (entry 4). Sparteine holds a prominent position in stereoselective reactions of organolithium reagents.[25] Yet, the use of (–)-sparteine and diene **21** (1:1) in the addition to **3** once again did not improve the diastereoselectivity (entry 5). Solvents other than THF, such as Et_2O and PhMe, were not suitable because of the insolubility of the La(III) salts. It has been noted that amine cosolvents can dramatically affect the distereoselectivity of organolithium additions to ketones.[26] However, addition of dienyllithium **21** to ketone **3** in mixtures of THF and amine bases such as Et_3N (entry 6) or TMEDA (entry 7) gave the same selectivity as observed before (dr = 1:1.2). In summary, all attempts to improve facial selectivity for the addition of dienyllithium **21** to **3** and its derivatives were unfruitful. As such, tertiary alcohol **22** was further elaborated.

The manipulation of the tertiary hydroxy group proved tricky in a number of respects for **22** as well as closely related structures. For example, attempts to acylate routinely resulted in elimination to give a triene. We also observed that the tertiary hydroxyl in **22** had a proclivity to form a cyclic imidate by addition to the nitrile, rendering introduction of a variety of protecting groups difficult. Finally, the reaction of **22** with Et_3SiCl/imidazole at 80 °C for 3.5 days furnished **23** in 81% yield.[27] Subsequent reduction of the nitrile group with DIBAL-H afforded aldehyde **24** (89%).[28]

Access to the Pentacyclic Framework. In principle, intramolecular [4+2] cycloaddition reaction involving a trisubstituted, olefinic dienophile would provide direct access to the completed decalyl subunit (Scheme 8). However, initial investigations deemed such a route untenable because of high temperatures required for cycloaddition (240 °C), which resulted in product mixtures. We reasoned that incorporation of an acetylenic dienophile could overcome the sluggish reactivity imposed by the 1,1-disubstitution of the unactivated diene.[29,30] As shown in Scheme 8, attempted cycloaddition of the corresponding 1-propynyl ketone gave only unsatisfactory results. This led us to consider alternative terminal groups at the ynone, which would satisfy two key criteria: sufficient activation to render efficient cycloaddition and its function as a placeholder for a methyl group. To this end, sulfonyl ynones are highly reactive in cycloaddition reactions[31] and the resulting sulfonyl enones readily undergo addition-elimination with alkyl cuprates.[32]

Addition of aldehyde **24** to lithiated alkyne **30** furnished secondary alcohol **31** in 93% yield (Scheme 9). In the next step, during the subsequent oxidation of **31** with DMP at room temperature, we observed concomitant formation of the Diels–Alder adduct.[33] Thus, a convenient one-pot procedure involving *in situ* oxidation and cycloaddition was carried out. Substitution of the sulfone using various methyl cuprates posed a challenge, owing to competing 1,2-addition and allylic oxidation. The use of Me_2CuLi in thoroughly degassed Et_2O was essential in a procedure that provides dienone **32** as a single diastereomer in 52% overall yield from **31**. No isomerization to the conjugated 1,3-diene was observed under the reaction conditions. Subsequent chemoselective reduction of the more electron-rich and accessible carbon-carbon double bond was achieved with Adams' catalyst under an atmosphere of hydrogen[34] to give enone **33** in 90% yield.

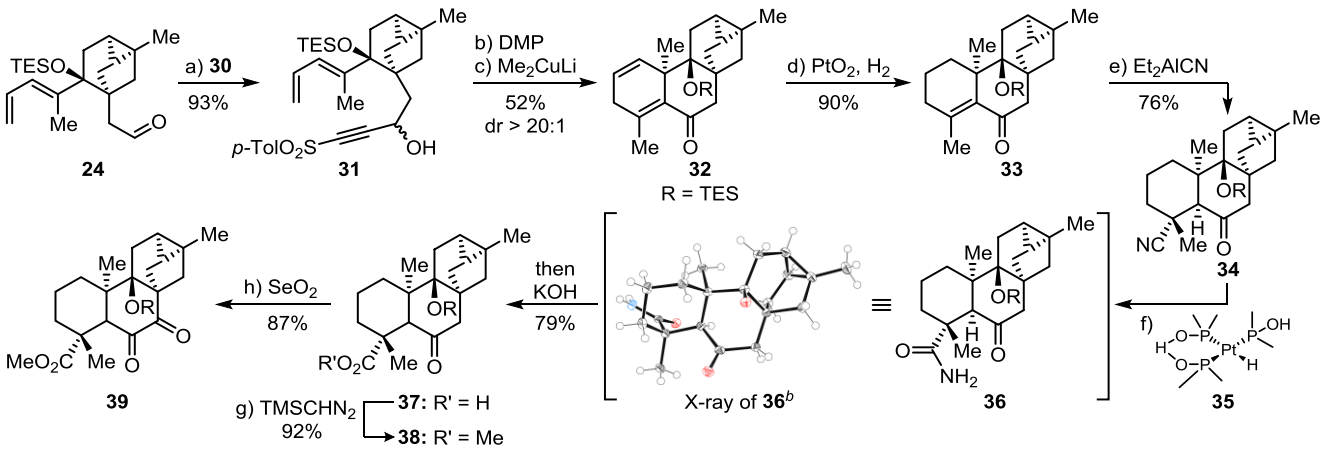
Scheme 8. [4+2] Cycloaddition Strategies and Dienophile Analysis



The next steps in the synthesis route were aimed at installation of the quaternary center that incorporates an ester. The inherent reactivity of α,β-unsaturated ketone **33** suggested conjugate addition of a methoxycarbonyl proxy. The neighboring silyl ether and tetrasubstituted carbon center create a sterically demanding periphery that complicated reactivity towards 1,4-addition. For example, no reaction was observed when enone **33** was treated with higher-order vinyl cuprate ($(C_2H_3)_2Cu(CN)Li_2$)[35] or an aluminum alkynylide ($Et_2AlCCTMS$).[36] Nagata's reagent (Et_2AlCN) has been commonly used in the hydrocyanation of hindered enones.[37] In our hands, desired ketonitrile was obtained as a separable mixture of diastereomers at the newly installed quaternary center (7.8:1 as determined by ^{1}H NMR of the unpurified product) from which **34** was isolated in 76% yield.

With nitrile **34** in hand, different pathways to access methyl ester **38** were explored. Alkaline conditions (KOH) resulted in loss of cyanide to return enone **33**. Ghaffar and Parkins previously reported the hydration of nitriles using $[PtH(PMe_2OH)((PMe_2O)_2H)]$ (**35**),[38] which exhibits high

Scheme 9. Construction of the Pentacyclic Framework of (–)-Mitrephorone A[a]



[a]Reagents and conditions: (a) ethynyl *p*-tolyl sulfone (**30**), LDA, THF, –78 °C, then **24**, 93% (dr = 2:1, inconsequential); (b) DMP, *t*-BuOH, RT; (c) Me_2CuLi, Et_2O, 0 °C, 52% (2 steps), dr > 20:1; (d) PtO_2 (10 mol%), H_2 (1 atm), EtOH, RT, 90%; (e) Et_2AlCN, PhMe, 0 °C, 76% **34**, 10% C_{quat}-*epi*-**34**; (f) Ghaffar–Parkins catalyst (**35**, 50 mol%), EtOH–H_2O (4:1), 80 °C, then KOH, 170 °C, 79%; (g) $TMSCHN_2$, PhH–MeOH (4:1), 0 °C to RT, 92%; (h) SeO_2, 1,4-dioxane, 100 °C, 87%. [b]Thermal ellipsoids displayed at 50% probability level. The triethylsilyl group on the tertiary alcohol was omitted for clarity.

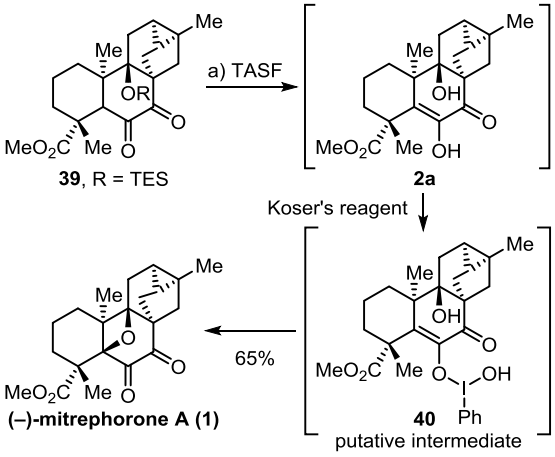
functional group tolerance and was shown to hydrolyze even hindered nitriles.[39] To our satisfaction, subjecting ketonitrile **34** to substoichiometric quantities of the homogenous Platinum catalyst in aqueous ethanol at 80 °C cleanly afforded the corresponding primary amide **36** (>95% yield).

Unfortunately, all initial attempts to convert the amide into the carboxylate failed. Although *O*-methylation using Meerwein's salt afforded the intermediate methyl imidate, it was reluctant to undergo hydrolysis to the targeted methyl ester.[40] In addition, various nitrosation methods ($NOBF_4$,[41] *t*-BuONO[42]) resulted only in decomposition of starting material. In contrast, subjecting amide **36** to KOH at 170 °C cleanly furnished carboxylic acid **37**.[43] This observation led us to the development of a one-pot hydration/hydrolysis procedure, affording **37** in 79% yield from **34**. Subsequent esterification with $TMSCHN_2$ ultimately provided methyl ester **38** in 92% yield.

Synthesis of (–)-Mitrephorone A. In setting the stage for oxidative cyclization to access the oxetane, the 1,2-diketone was installed next. Riley oxidation of ketone **38** using SeO_2 efficiently furnished α-diketone **39** in 87% yield.[44,45] Deprotection of the hindered silyl ether in **39** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) cleanly gave tertiary alcohol **2a** as the tautomeric enol ketone in 82%.[46] Oxetane formation was envisioned to involve conjugate addition of the hydroxy group to the enone followed by oxidation. In the context of previously reported iodine(III)-mediated oxidative cyclizations,[47] we reasoned that ligand exchange at $ArIX_2$ by enol in **2a** could trigger the targeted *4-exo-trig* cyclization.[48] In practice, one-pot deprotection of silyl ether **39** (TASF) and subsequent reaction with Koser's reagent (PhI(OH)OTs) proved successful and completed the total synthesis of (–)-mitrephorone A (Scheme 10). The spectroscopic data (^1H NMR, ^{13}C NMR, IR, $[\alpha]_D$) and high-resolution mass collected for **1** were in full agreement with that reported for the natural product.

Along with **1**, Oberlies and coworkers isolated (–)-mitrephorone B (**2b**), which prominently features a diosphenol and lacks the tertiary hydroxy group present in **2a**. No biosynthetic pathways have been proposed for any member of the mitrephorone family. Our observation that **2a** undergoes facile oxidative ring closure using iodine(III) suggests that biooxidation of a hydroxy diosphenol may be operative.

Scheme 10. Completion of the Total Synthesis[a]



[a]Reagents and conditions: (a) TASF, H_2O, DMF, 0 °C, then PhI(OH)OTs, 65%.

Conclusion

In conclusion, we have reported the first and enantioselective synthesis of (–)-mitrephorone A. The intramolecular Diels–Alder reaction of 5-vinyl-1,3-cyclohexadiene intermediate **11** enabled rapid construction of the characteristic tricyclo[3.2.1.$0^{2,7}$]octane core. The use of a highly reactive β-sulfonyl alkynone *en route* to dienone **32** efficiently furnished the pentacyclic carbon framework of the natural product. A pivotal feature of this synthesis is the oxidative cyclization with hypervalent iodine to generate an embedded oxetane. In a broader sense, formation of four-membered oxacycles from the corresponding hydroxy diosphenols has no precedence and thus ex-

tends known approaches for the synthesis of oxetanes that include alkylations, rearrangements, [2+2] cycloadditions, and haloetherifications.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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