Enantioselective Synthesis of [3]-Ladderanol through a Late-Stage Organocatalytic Desymmetrization

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Abstract: Ladderane phospholipids, with their unusual ladder-like arrangement of fused cyclobutane rings, represent an architecturally unique class of natural products. However, despite their fascinating structure and other necessary impetus, only a few synthetic studies of these molecules have been reported so far. We have now devised a concise synthesis of [3]-ladderanol, a component of ladderane phospholipids, using an organocatalytic enantioselective desymmetrizing formal C(sp^2)–H alkylation. Our synthetic strategy rests on a late-stage introduction of chirality, thus allowing facile access to both the enantiomers of [3]-ladderanol as well as its analog. This is the first time a desymmetrization strategy is applied to the synthesis of [3]-ladderanol. The scope of this desymmetrizing C(sp^2)–H alkylation of *meso*-cyclobutane fused cyclohexenediones is also presented.

Introduction

Architecturally unique natural products have always captivated organic chemists and inspired the development of new synthetic tools for achieving those targets.[1] Isolation of ladderane phospholipids **1**-**2** (Figure 1) in 2002 from anerobic ammonium oxidizing (anammox) bacteria revealed such never-seen-before structural features in nature.[2] These molecules were named so due to the presence of highly unusual ladder-like arrangements of concatenated cyclobutane rings.[3]

The perceived function of the anammox bacteria is as fascinating as the structure of these lipids. In a large intracellular compartment of these bacteria, known as the anammoxosome, ammonium and nitrite are coupled to produce dinitrogen in an overall exergonic reaction called the anammox process.[4] The presence of ladderane phospholipids into the membrane of anammoxosome imparts unusual density, which helps in maintaining a pH gradient across the membrane that drives ATP synthesis.[5]

Due to the slow growth rate of the producing organism and the inherent difficulty in purifying such complex lipid mixtures,[6] laboratory synthesis remains the primary source of ladderane phospholipids for studying the relationship between their structure and biological function.

As shown in Figure 1, these ladderane phospholipids are composed of either (+)-[3]-ladderanol (**3**) or a mixture of (+)-[3]-ladderanol (**3**) and (–)-[5]-ladderanoic acid (**4**).[7] While several strategies were conceived for the construction of non-natural ladderanes prior to 2002,[8] only a few research groups have invested into the synthesis of naturally occurring ladderane phospholipids so far.[9] [5]-Ladderanoic acid (**4**) was the first member of the ladderane family of natural products to be synthesized. The pioneering synthesis by Corey et al. in 2004 resulted **4** in racemic form.[10] Soon after, the same group disclosed the synthesis of (+)-[5]-ladderanoic acid [(+)-**4**] using a diastereoselective photochemical [2+2]-cycloaddition.[11] More than a decade after these initial reports, Burns[12] and Brown[13] groups synthesized both [3]-ladderanol (**3**) and [5]-ladderanoic acid (**4**). Burns et al. went on to assemble (+)-**3** and (–)-**4** into phospholipid **1** and established its absolute configuration.[12]

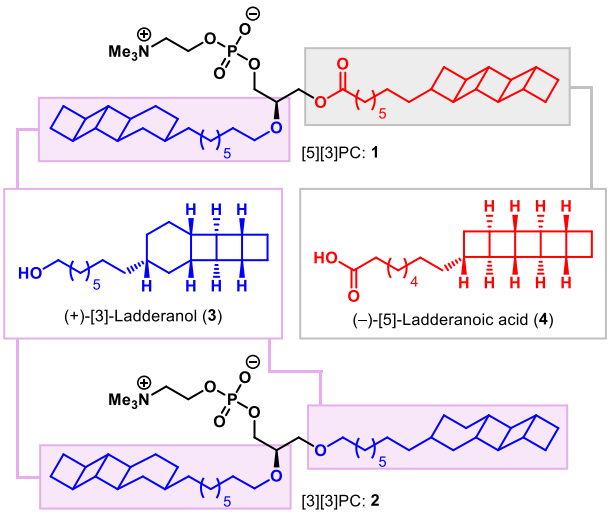
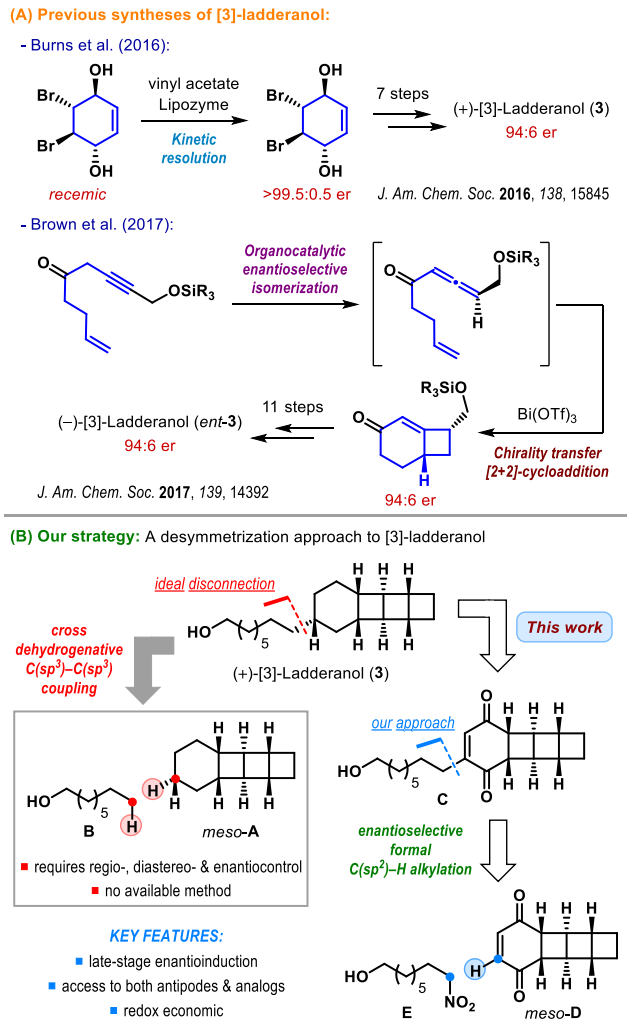


Figure 1. Natural ladderane phospholipids and their tail groups. PC denotes phosphatidylcholine.

While both Burns' and Brown's elegant syntheses of [5]-ladderanoic acid (**4**) made use of the symmetry of the [5]-ladderane core itself[12] or its lower member,[13a] a desymmetrization route to [3]-ladderanol (**3**) has never been realized. Burns' synthesis of (+)-**3** begins with a lipase-resolved enantiopure dibromodiol[12] whereas Brown's strategy to (–)-**3** hinges on an organocatalytic enantioselective isomerization of a deconjugated alkynyl ketone, followed by an intramolecular chirality transfer [2+2]-cycloaddition of the resulting chiral allenone[13b] (Scheme 1A). In both these syntheses, the enantioinduction takes place at the early phase of the synthetic route and is carried forward through the rest of the steps.

We sought to devise a strategy for the enantioselective synthesis of [3]-ladderanol by exploiting the symmetry of its tetracyclododecane skeleton and doing so with the direct installation of the linear 8-carbon alkyl chain in the desymmetrization step. Such an approach would allow for the introduction of chirality at a very late stage of the synthesis and provide the flexibility – not just in accessing both the enantiomers of [3]-ladderanol but also in modulating its structure for further studies.



Scheme 1. Previous syntheses of [3]-ladderanol and our synthetic strategy

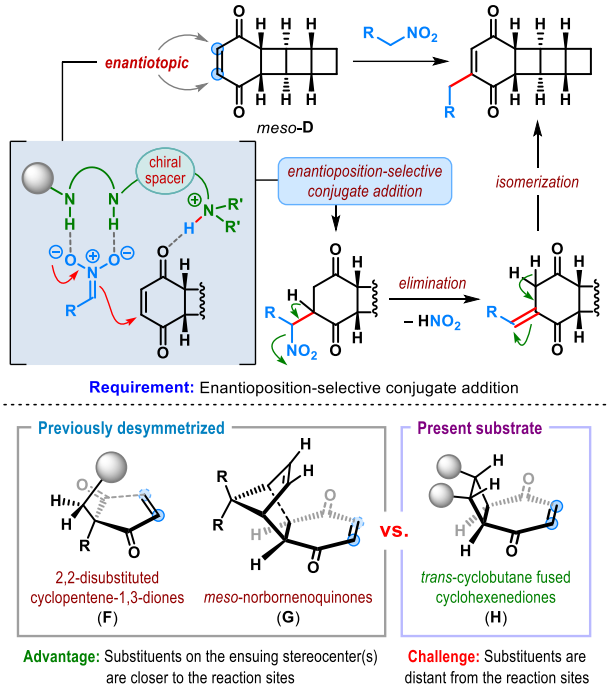
A direct desymmetrizing cross-dehydrogenative C(sp^3)– C(sp^3) coupling[14] between *meso*-tetracyclododecane **A** and 1-octanol **B** would constitute an ideal synthesis of [3]-ladderanol (Scheme 1B). However, a regio-, diastereo- and enantioselective coupling reaction of this kind poses a daunting challenge, and no such method is currently available at chemists' disposal.

Our deliberation along the same line of retrosynthetic analysis, instead, led us to a more realistic disconnection using tetracyclic *meso*-cyclohexenedione **D** as a synthon of **A** (Scheme 1B). We have previously developed enantioselective desymmetrizations of related prochiral or *meso*-enediones by organocatalytic formal C(sp^2)–H alkylation using nitroalkanes as the alkylating agent.[15] Accordingly, we envisioned a direct coupling between 8-nitrooctan-1-ol **E** and *meso*-**D** for the enantioselective synthesis of the entire [3]-ladderanol framework **C**. The remainder of the synthesis could then be accomplished by diastereoselective hydrogenation and deoxygenation of **C**.

Herein we present a systematic implementation of this strategy, which eventually culminated in the total synthesis of both the enantiomers of [3]-ladderanol as well as an analog.

Although our previously developed desymmetrizing formal C(sp^2)–H alkylation of enediones[15] formed the basis of this synthetic strategy, we were cognizant of the potential challenges posed by *meso*-**D** and related *trans*-cyclobutane fused polycyclic cyclohexenediones. In this reaction, stereocenters are generated remote from the reaction site[16] and enantioposition-selective conjugate addition of nitronate is the key to its success (Scheme 2). Compared to both 2,2-disubstituted cyclopentene-1,3-diones (**F**) and *meso*-norbornenoquinones (**G**), the substituents in *trans*-cyclobutane fused polycyclic cyclohexenediones (**H**) distance

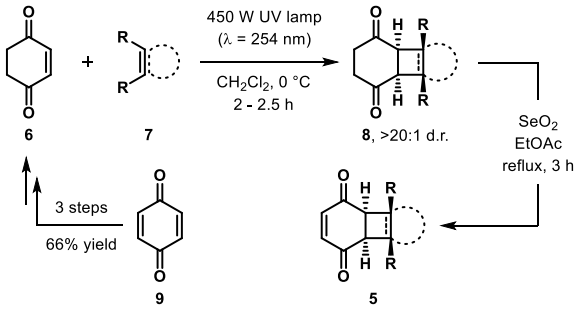
themselves further from the reactive centers and hence, from the catalyst. This structural feature renders the crucial enantioposition-selective addition even more challenging.



Scheme 2. Requirement for the key enantioselective formal C(sp^2)–H alkylation and the challenge posed by the present substrate

Results and Discussion

To identify the optimum catalyst and reaction conditions for the enantioselective formal C(sp^2)–H alkylation, we began our investigation with a model substrate – tricyclic *meso*-cyclohexenedione **5a**, considering its easier accessibility and structural resemblance with **D** (Table 1). These cyclobutane fused *meso*-cyclohexenediones (**5**) can be prepared by [2+2]-photocycloaddition between cyclohexenedione **6** and an appropriate *cis*-alkene or alkyne **7**, followed by dehydrogenation with SeO_2 (Scheme 3).[17] These [2+2]-photocycloaddition reactions of alkenes were seen to proceed usually in good yield and with complete *exo*-selectivity. Cyclohexenedione **6** can in turn be obtained from *p*-benzoquinone **9**.[18]



Scheme 3. Preparation of cyclobutane fused *meso*-cyclohexenediones **5**

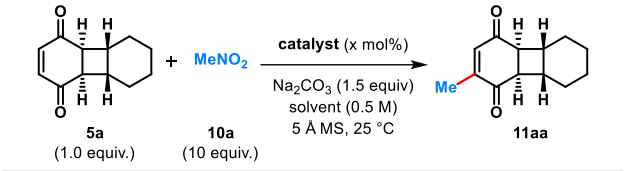
Initial optimization studies for C(sp^2)–H alkylation were carried out using nitromethane (**10a**) as the alkylating agent.[19] When the reaction was carried out in $CHCl_3$ with 10 mol% quinine-derived bifunctional tertiary aminothiourea **I** as the catalyst[20] and Na_2CO_3 as the terminal base, the desired C–H methylated product **11aa** was formed in 41% yield with a promising enantiomeric ratio (e.r.) of 92:8 (Table 1, entry 1). A slight improvement in yield and enantioselectivity was observed using the corresponding squaramide **II** as the catalyst[21] (entry 2). The enantioselectivity of this reaction turned out to be somewhat independent of the reaction medium (entries 4-6). However, lowering the initial concentration led to an enhancement in e.r. (entry 7). An attempt to improve the reaction rate and e.r. by increasing the catalyst loading proved futile (entry 8). Instead, a reduction in catalyst loading surprisingly resulted in the rate enhancement while maintaining the same level of enantioselectivity (entry 9). The reaction can be scaled up under these conditions, when **11aa** was isolated in 75% yield with 95:5 e.r. (entry 10).

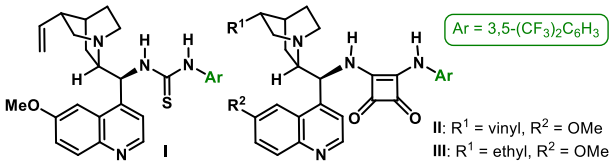
We were pleased to note that the catalyst and reaction conditions optimized for the formal C(sp^2)–H methylation of tricyclic *meso*-cyclohexenedione **5a** could be successfully extrapolated to a variety of polycyclic *meso*-cyclohexenediones **5** (Table 2A). These examples not only include *trans*-cyclobutane fused tri- (**5a**-**d**) and tetracyclic substrates (**5h**-**i**) but also to bicyclic cyclohexenediones

(**5e**-**g**). The products (**11aa**-**ia**) were generally isolated in moderate to good yield with modest enantioselectivity in most cases. Enantioenrichment of some of these products (**11ca**, **11ha**) is possible with up to 98:2 e.r. by a single recrystallization. Most notably, our coveted tetracyclic *meso*-cyclohexenedione **5i** could be desymmetrized efficiently, and the product **11ia** was obtained with good enantioselectivity, especially after recrystallization.

Overall, the level of enantioselectivity observed in this reaction is considerably lower compared to 2,2-disubstituted cyclopentene-1,3-diones **F** and norbornenoquinones **G** (Scheme 2).[15] Barring **11ca** which appears as an anomaly, the presence, or the absence of the *trans*-substituents on the fused cyclobutane ring imparted little influence on the enantioposition-selectivity (cf. **11ea** and **11ia**). This observation is in agreement with our anticipation and corroborated by the solid-state structure of the products **11ha**-**ia** (CCDC 2144865-6, Table 2),[22] where the *trans*-substituents reside far from the reaction site. The product **11fa**, bearing two *cis*-methyl groups on the cyclobutane, on the other hand, was obtained with relatively higher e.r. Along the same line, the planar cyclobutene in **5g** expectedly offered less steric crowding and resulted in **11ga** with much inferior e.r.

Table 1. Optimization of catalyst and reaction conditions for enantioselective formal C(sp^2)–H methylation of tricyclic *meso*-cyclohexenedione **5a**.[a]





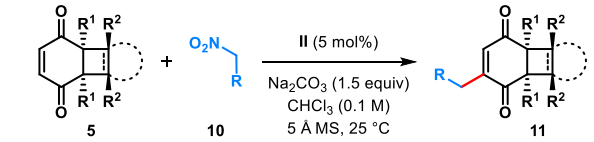
Entry	Catalyst [x]	Solvent	*t* [h]	Yield [%][b]	e.r.[c]
1	**I** [10]	$CHCl_3$	48	41	92:8
2	**II** [10]	$CHCl_3$	48	45	93:7
3	**III** [10]	$CHCl_3$	48	45	92.5:7.5
4	**II** [10]	toluene	48	48	93:7
5	**II** [10]	CH_2Cl_2	48	40	93:7
6	**II** [10]	THF	48	28	92:8
7[d]	**II** [10]	$CHCl_3$	96	67	95:5
8[d]	**II** [20]	$CHCl_3$	120	70	95:5
9[d]	**II** [5]	$CHCl_3$	72	70	95:5
10[d,e]	**II** [5]	$CHCl_3$	96	(75)	95:5

[a] Reactions were performed using 1.0 equiv of **5a** and 10 equiv of **10a** on a 0.1 mmol scale. [b] Yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield is given in the parentheses. [c] Enantiomeric ratio (e.r.) as determined by HPLC analysis using a stationary phase chiral column. [d] Reaction at 0.1 M initial concentration. [e] Reaction on a 0.3 mmol scale.

The introduction of higher alkanes is also possible. However, as seen in our earlier studies,[15] the reactions with higher nitroalkanes (**10b**-**d**) were found to be slower and proceeded with inferior enantioselectivities (Table 2B).

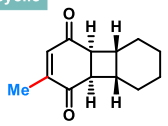
Nonetheless, the amenability of these reaction conditions to tetracyclic *meso*-cyclohexenedione **5i** and the possibility of using higher nitroalkanes, especially **10d**, provided us the necessary incentive to attempt the direct installation of the linear 8-carbon alkyl chain through this enantioselective formal C(sp^2)–H alkylation reaction. Once again, our initial studies in this direction were focused on the model substrate **5a**.[19] Interestingly, the reaction of **5a** with *O*-protected 8-nitrooctan-1-ols (**10e**-**f**) under our optimum reaction conditions (Table 2) resulted in the Michael adducts **12ae**-**af**,[23] which were isolated as a single diastereomer (Scheme 4A). The isolation of these Michael adducts momentarily gave rise to the possibility of accessing [3]-ladderanol through reductive denitration[24] and deoxygenation by following a similar route with **5i**. Unfortunately, determination of absolute stereochemistry of **12ae** through single crystal X-ray diffraction analysis (CCDC 2144867, Scheme 4A)[22] revealed the formation of the undesired diastereomer in this reaction and forced us to stick to our original plan (Scheme 1B). Although the desired C(sp^2)–H alkylated product **11** could be obtained with excellent enantioselectivity by treating **12** with a combination of KOAc and 18-crown-6, the abysmal yield of this two-step process prohibited us from applying it to the synthesis of [3]-ladderanol.

Table 2. Scope of enantioselective formal C(sp^2)–H alkylation of cyclobutene-fused cyclohexenediones.[a]

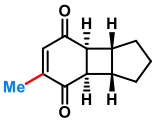


(A) Scope of Cyclohexenediones

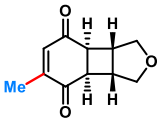
Tricyclic



11aa
96 h, 75% yield
95:5 e.r.

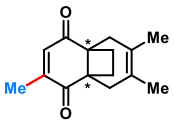


11ba
120 h, 72% yield
92.5:7.5 e.r.

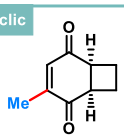


11ca[b]
96 h, 64% yield
86.5:13.5 e.r. (98:2 e.r.)

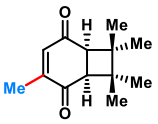
Bicyclic



11da
120 h, 80% yield
90:10 e.r.

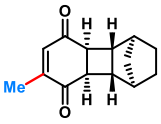


11ea
72 h, 60% yield
90:10 e.r.

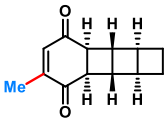


11fa
120 h, 50% yield
95:5 e.r.

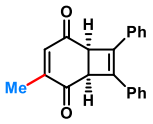
Tetracyclic



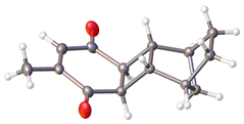
11ha[b]
120 h, 66% yield
93:7 e.r. (98:2 e.r.)



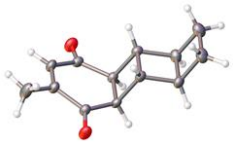
11ia[b]
84 h, 67% yield
91:9 e.r. (95:5 e.r.)



11ga
96 h, 94% yield
72:28 e.r.

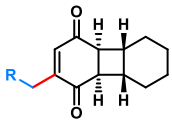


11ha
(CCDC 2144865)



11ia
(CCDC 2144866)

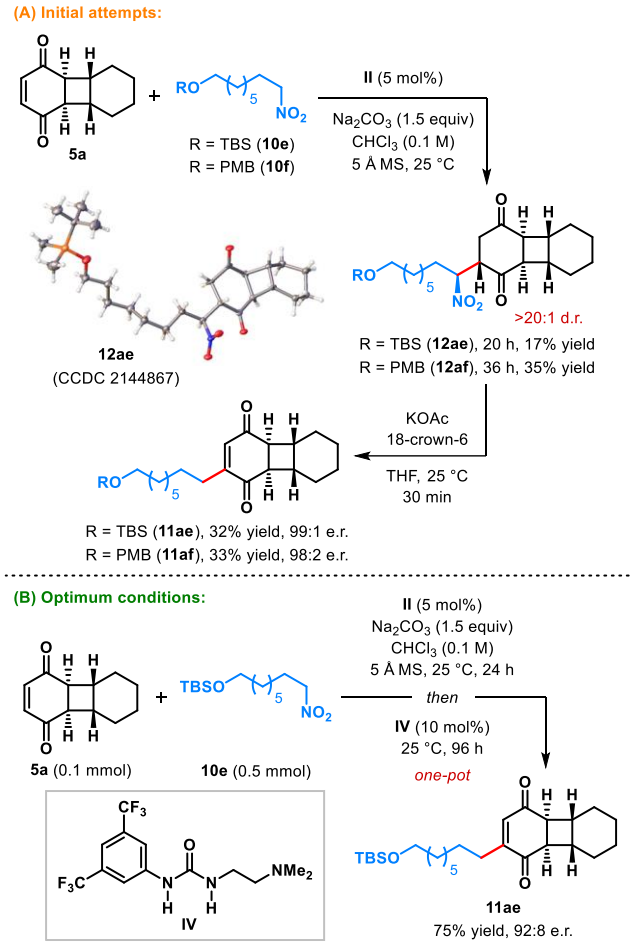
(B) Scope of Nitroalkanes



Entry	R (**11**)	*t* [h]	Yield [%]	e.r.
1	Me (**11ab**)	120	23	74:26
2	Ph (**11ac**)	120	50	92:8
3	CH_2OTBS (**11ad**)	120	62	90:10

[a] Reactions were carried out on a 0.3 mmol scale with either 10 equiv (**10a**-**b**) or 5 equiv (**10c**-**d**) of nitroalkanes and 50 mg 5 Å MS in a sealed vial. Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratio (e.r.) as determined by HPLC analysis using a stationary phase chiral column. [b] The numbers in the parentheses represent e.r. after a single recrystallization.

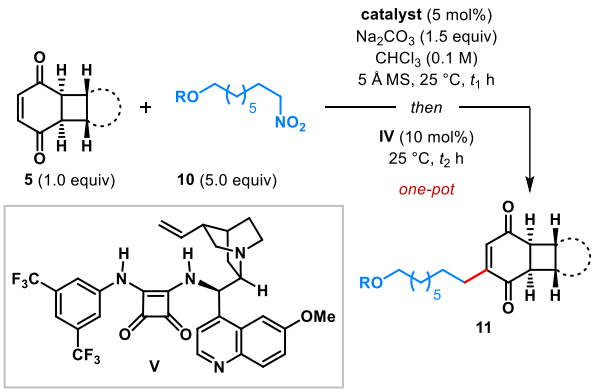
A detailed optimization of catalyst and reaction conditions resulted in a one-pot two-step protocol using two different bifunctional catalysts – one for each step. While the quinine-derived tertiary aminosquaramide **II** was efficient for the enantioposition-selective Michael addition, the elimination of HNO_2 and isomerization were found to be slow under its influence. These latter steps proceeded relatively faster with the achiral tertiary aminourea **IV** (Scheme 4B). Under these conditions, **11ae** was isolated in 75% yield with 92:8 e.r.



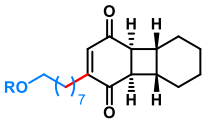
Scheme 4. Installation of 8-carbon alkyl chain through enantioselective formal C(sp^2)–H alkylation

This one-pot two-step protocol was then applied to both the model substrate **5a** (Table 3A) and the tetracyclic *meso*-cyclohexenedione **5i** (Table 3B) with differently protected (**10e**-**f**) and even unprotected 8-nitrooctan-1-ol (**10g**). In the case of *O*-protected 8-nitrooctan-1-ols (**10e**-**f**), the products (**11ae**-**af**, **11ie**-**if**) were generally obtained in good yield with decent enantioselectivities. However, lower yields and enantioselectivities were observed when the reactions were carried out with 8-nitrooctan-1-ol **10g**. We were pleased to note the formation of the other product antipode with the same level of enantioselectivity in most cases when **II** was replaced by pseudoenantiomeric tertiary aminosquaramide **V**, derived from quinidine. These reactions could be performed on a larger (0.5 mmol) scale without significantly compromising the outcome. Although a large excess (5 equiv) of nitroalkanes (**10e**-**g**) had to be used in these reactions for achieving a reasonable reaction rate, most of the unreacted nitroalkanes (3.6-3.9 equiv) could be recovered and reused.

Table 3. Installation of 8-carbon alkyl chain: Scope[a]

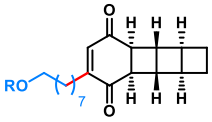


(A)



R (**11**)	Cat.	t_1 [h]	t_2 [h]	Yield [%]	e.r.
TBS (**11ae**)	**II**	24	96	75	92:8
TBS (**11ae**)	**V**	24	96	74	8:92
TBS (**11ae**)[b]	**II**	72	120	77	92:8
PMB (**11af**)	**II**	32	96	63	91.5:8.5
H (**11ag**)	**II**	90	96	63	90:10

(B)

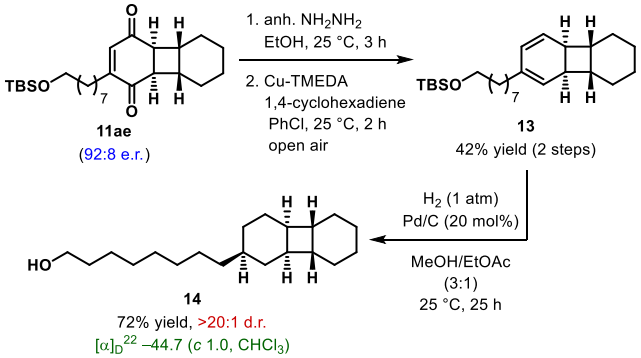


R (**11**)	Cat.	t_1 [h]	t_2 [h]	Yield [%]	e.r.
TBS (**11ie**)	**II**	24	48	71	90:10
TBS (**11ie**)	**V**	24	48	70	10:90
TBS (**11ie**)[b]	**V**	54	96	69	10:90
PMB (**11if**)	**II**	48	72	58	94.5:5.5
PMB (**11if**)	**V**	48	72	63	11:89
PMB (**11if**)[b]	**II**	48	72	71	91:9
H (**11ig**)	**II**	68	60	47	87.5:12.5
H (**11ig**)	**V**	68	60	44	18:82

[a] Unless stated otherwise, reactions were carried out on either 0.2 (Table 3A) or 0.05 mmol scale (Table 3B). Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratio (e.r.) as determined by HPLC analysis using a stationary phase chiral column. [b] Reaction on a 0.5 mmol scale. TBS = *tert*-Butyldimethylsilyl; PMB = *p*-Methoxybenzyl.

After assembling the entire carbon-skeleton (**11ie**-**ig**) of [3]-ladderanol, only the complete reduction of the enedione functionality was left for achieving its total synthesis. We once again chose the model compound **11ae** to probe our synthetic strategy. Our initial plan involved a diastereoselective hydrogenation of the olefin followed by ketone reduction and deoxygenation of the corresponding mesylate derivative. However, unexpected complications compelled us to abandon this and related strategies.[19] We, instead, chose to adopt Burns' endgame[12] for completing the total synthesis.

Accordingly, **11ae** was transformed into 1,3-cyclohexadiene derivative **13** by Cu-TMEDA-mediated denitrogenation of the initially prepared bis-hydrazone (Scheme 5). Hydrogenation of the diene **13** under Pd/C proceeded diastereoselectively and was accompanied by the deprotection of the TBS group to furnish [3]-ladderanol analog **14** as a single diastereomer in 72% isolated yield.

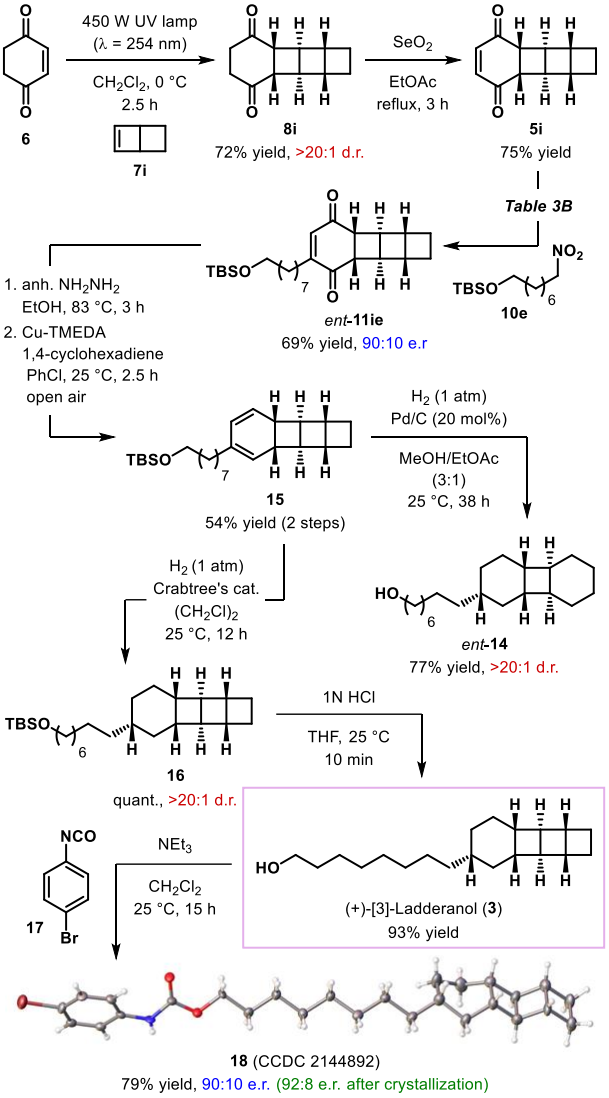


Scheme 5. Elaboration of desymmetrized tricyclic cyclohexenedione **11ae** to [3]-ladderanol analog **14**

With necessary groundworks done, the stage was set to complete the enantioselective synthesis of [3]-ladderanol. As discussed above (Scheme 3) and illustrated in Scheme 6, our key building block *meso*-cyclohexenedione **5i** was assembled from cyclohexene-1,4-dione **6** and bicyclohexene **7i**. Desymmetrization of **5i** by enantioselective formal C(sp^2)–H alkylation with TBS-protected 8-nitrooctan-1-ol (**10e**) was accomplished using a sequential combination of tertiary aminosquaramide **V** and tertiary aminourea **IV**, as

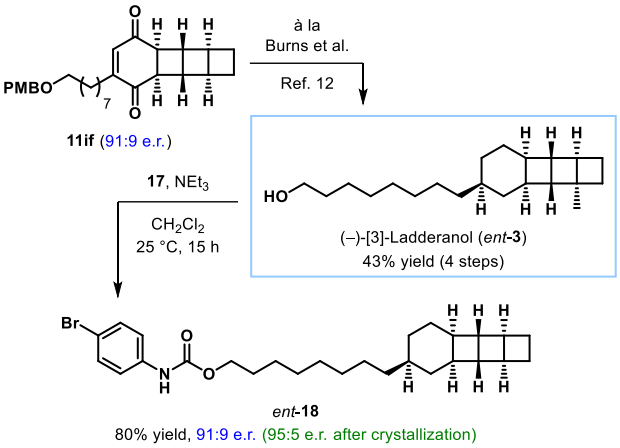
described in Table 3B. The product *ent*-**11ie**, having the entire carbon-skeleton of natural [3]-ladderanol with the correct stereochemistry at the fused ring junctions, thus obtained with 90:10 e.r., was then subjected to the two-step deoxygenation protocol developed by Burns et al.[12] The resulting 1,3-cyclohexadiene derivative **15** was isolated in an overall yield of 54% over two steps. Although the analogous 1,3-cyclohexadiene **13** could be hydrogenated diastereoselectively under Pd/C (see Scheme 5), subjecting **15** to this heterogeneous reaction conditions caused fragmentation of the strained tetracyclododecane ring to generate tricyclododecane derivative *ent*-**14**, albeit as a single diastereomer, in good yield. Hydrogenation under homogeneous conditions using Crabtree's catalyst [Ir(COD)(PCy_3)(py)]PF_6, on the other hand, quantitatively converted **15** to the desired diastereomer **16** without affecting the ladderane motif. Deprotection of the TBS group with aqueous HCl concluded the total synthesis of (+)-[3]-ladderanol **3** – a component of the natural ladderane phospholipids.

Conversion of **3** to the corresponding *p*-bromophenyl carbamate **18** facilitated the growth of single crystals suitable for X-ray diffraction analysis (CCDC 2144892, Scheme 6)[22] and further confirmed the absolute configuration of (+)-[3]-ladderanol.



Scheme 6. Enantioselective total synthesis of (+)-[3]-ladderanol (**3**)

The introduction of chirality at a later stage renders flexibility to our synthetic route. We chose to demonstrate the advantage of this modular approach by synthesizing the non-natural antipode of [3]-ladderanol *ent*-**3** (Scheme 7). This time we decided to use the PMB-protected desymmetrized tetracyclic cyclohexenedione **11if**, an intermediate in Burns' synthesis,[12] which we could prepare with 91:9 e.r. (see Table 3B). Starting from **11if**, following Burns' protocol,[12] (–)-[3]-ladderanol *ent*-**3** was synthesized in 43% yield over four steps. As shown with (+)-[3]-ladderanol (Scheme 6), in this case also enantioenrichment of the corresponding *p*-bromophenyl carbamate (*ent*-**18**) could be achieved after a single recrystallization.



Scheme 7. Elaboration of **11if** to (–)-[3]-ladderanol (*ent*-**3**)

Conclusion

In conclusion, we have accomplished an enantioselective total synthesis of [3]-ladderanol. Our synthetic strategy rests on a conceptually novel direct enantioselective assembly of the linear alkyl chain with the tetracyclododecane core of [3]-ladderanol. In practice, this intricate task is realized through a desymmetrizing formal C(sp^2)–H alkylation of tetracyclic *meso*-cyclohexenedione – the tetracyclododecane core at a higher oxidation state. This one-pot two-step C–C bond forming transformation, utilizing *O*-protected 8-nitrooctan-1-ol as an air and moisture-stable alkyl sources, is catalyzed by a sequential combination of a chiral tertiary aminosquaramide and an achiral tertiary aminourea. This is the first time an enantioselective desymmetrization strategy is applied to the synthesis of [3]-ladderanol. The late-stage introduction of chirality offers flexibility to this already concise route, which allowed for the synthesis of both the enantiomers of [3]-ladderanol as well as its analog with a good level of enantioselectivity.

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