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Introduction

(*–*)-Morphine (**1**) is one of the oldest and most extensively used analgesics which led it, along with its congeners (*–*)-codeine (**2**) and (*–*)-thebaine (**3**), to garner significant attention from numerous organic chemists as targets for synthesis (Fig. 1).¹ Extensive modifications to the naturally occurring opioids have also been investigated in endeavors to increase potency and *in vivo* efficacy and have led to the discovery of semi-synthetic opioids such as (*–*)-ketorfanol (**4**)² and the extensively prescribed (*–*)-oxycodone (**5**).³ However, despite the medical importance of naturally occurring and semi-synthetic opioid agonists, undesired side effects such as addictive properties and the potential for fatal overdoses are enormous societal problems. Therefore, semi-synthetic opioid antagonists were developed to address these growing problems.⁴ Naltrexone (**6**) was first patented in 1967 (ref. 5) and is currently an important treatment option for opioid abuse and alcohol dependence.⁴ The C-14 hydroxyl and *N*-cyclopropylmethyl substituent are essential structural features that are important for (*–*)-naltrexone's potency and antagonistic properties.⁴

The prevalent commercial routes to (*–*)-naltrexone (**6**) employ the natural product (*–*)-thebaine (**3**) as the starting

material. A number of strategies have been developed for exchange of the *N*-methyl for an *N*-cyclopropylmethyl group.⁶

Hudlicky has extensively investigated this step,⁷ including a particularly efficient alkylation and demethylation sequence of the thebaine derivative oripavine to give **9** (Fig. 2).^{7c} The dienol ether functionality present in (*–*)-thebaine allows for the straightforward introduction of the C-14 hydroxyl group by oxidative methods. For example, in Hudlicky's sequence, the dienol ether functionality in **9** was epoxidized followed by *in situ* oxirane ring opening to generate enone **10** followed by hydrogenation to give (*–*)-naltrexone (Fig. 2).⁸ Rice has also reported a semi-synthesis of the (+)-enantiomer of naltrexone. His

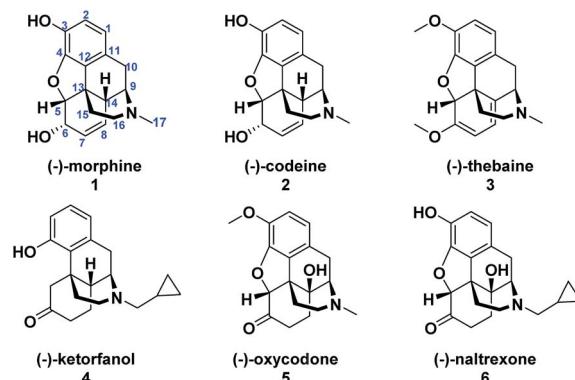
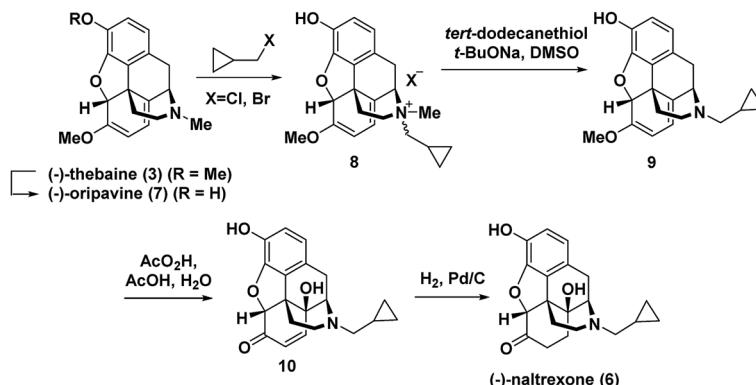


Fig. 1 Representative naturally occurring opioids (**1–3**) and semi-synthetic opioid agonists (**4–5**) and an antagonist (**6**).



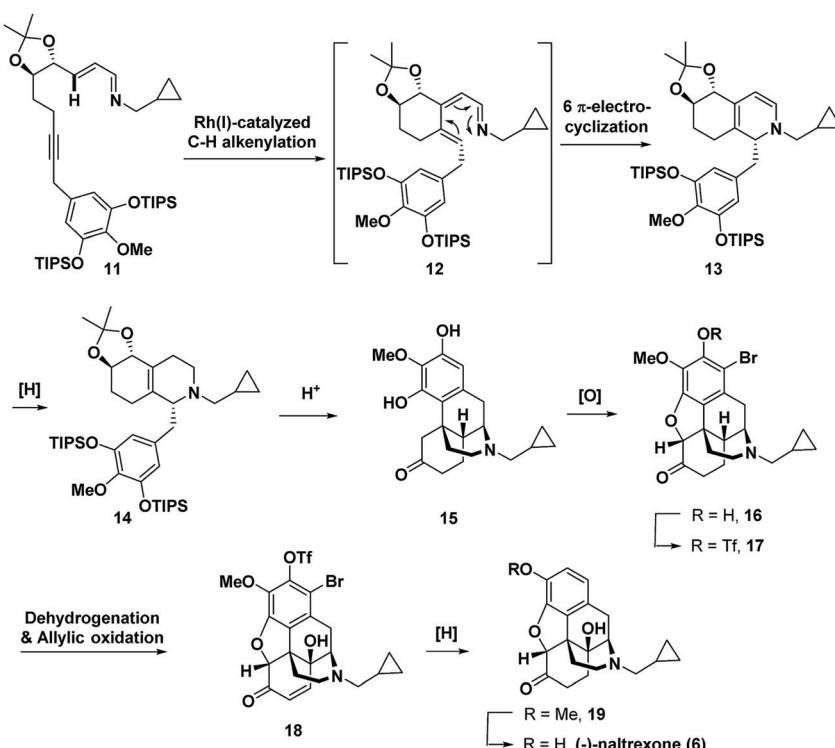
Fig. 2 Hudlicky's semi-synthesis of (-)-naltrexone.^{7c}

synthesis proceeded through (+)-thebaine, which was prepared in five steps from the natural product (+)-sinomenine as an innovative starting material.⁹

(-)Thebaine is currently isolated from opium poppies but is only a minor component of opium (0.3–1.5%), and poppy farming is problematic due to illicit drug activities.¹⁰ An alternative synthetic route that bypasses (–)-thebaine and starts with commercially available achiral precursors would provide novel entry to (–)-naltrexone. Moreover, starting from simple inputs should enable the investigation of a variety of analogs not accessible from more fully elaborated and densely functionalized morphinan natural products like (–)-thebaine.¹¹

Recently, we reported the synthesis of the unnatural enantiomer of the opioid agonist (+)-ketorfanol (4) (Fig. 1) using

a Rh(i)-catalysed C–H alkenylation and torquoselective 6- π electrocyclization cascade as a key step in the sequence.¹² Herein, we further apply this cascade approach to the synthesis of the considerably more complex opioid antagonist (–)-naltrexone (6) (Scheme 1). Imine 11 is efficiently prepared from achiral starting materials with catalytic asymmetric dihydroxylation used to introduce the stereogenic centers. Intramolecular Rh(i)-catalysed alkenylation to give azatriene 12 is followed by *in situ* torquoselective electrocyclization to set the desired stereochemistry in bicyclic hexahydroisoquinoline 13, which is reduced to obtain 14 as a single diastereomer. Acid treatment provides the tetracyclic morphinan 15 by concomitant removal of the protecting groups, Grewe cyclization and redox neutral conversion of the diol to the desired keto group.



Scheme 1 Approach to (–)-naltrexone from simple, achiral precursors.



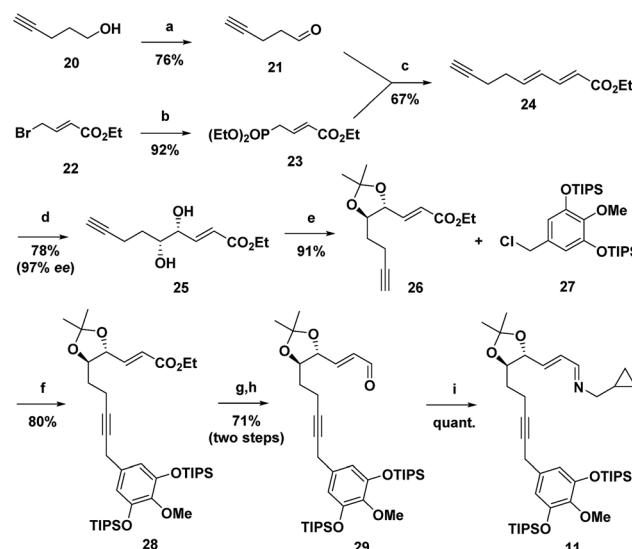
The 4-methoxy-3,5-disilyloxy substitution pattern on the phenyl ring of **14** was designed to allow for incorporation of the required aromatic ring oxygen substitution pattern while simultaneously ensuring that Grewe cyclization occurs without the possibility of generating regiosomeric products (*vide infra*).^{1f} The pentacyclic ether **16** is then obtained from tetracyclic **15** by treatment with Br_2 in AcOH according to methods developed for the synthesis of codeine.¹³

For intermediate **16**, installation of the hydroxyl group at C-14 would most efficiently be accomplished by dehydrogenation to an enone followed by C-H γ -hydroxylation. However, in syntheses of morphinan natural products such as morphine and codeine, researchers have found that for the efficient dehydrogenation of 6-keto derivatives to enones the nitrogen must be protected by an electron withdrawing carbamoyl or sulphonamide rather than an *N*-alkyl group as is present in **16**.^{1g,1h,14} Therefore, to enable dehydrogenation and γ -hydroxylation of **16** without the protection of the nitrogen, a Pd-mediated dehydrogenation method and $\text{Cu}(\text{II})$ -catalysed O_2 -mediated allylic C-H oxidation conditions were developed. Alkene hydrogenation with concomitant reductive cleavage of both the triflate and the bromide in **18** gave **19**, which upon demethylation provided (–)-naltrexone in 17 steps for the longest linear sequence. Because the stereochemistry is set by asymmetric catalytic dihydroxylation, the same route could equally be employed to prepare the (+)-enantiomer of naltrexone, which has been reported to have antagonist activity toward Toll-like receptor 4.¹⁵

Results and discussion

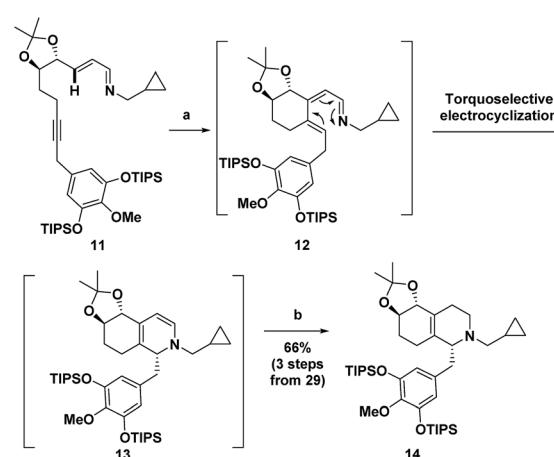
The synthesis commenced with the preparation of imine **11** in seven steps from simple achiral starting materials (Scheme 2). Horner–Wadsworth–Emmons (HWE) reaction of aldehyde **21** and phosphonate **23** afforded **24** in 67% yield. Based upon a report by Takacs,¹⁶ we found that use of $\text{LiOH} \cdot \text{H}_2\text{O}$ as the base in the presence of 4 Å molecular sieves minimized competitive self-condensation of aldehyde **21** and thus provided the most robust and reproducible HWE reaction conditions particularly on larger scales. Highly regio- and enantioselective dihydroxylation with AD-mix- β followed by protection of the diol as an acetonide gave **26** in high overall yield. The benzyl chloride **27**, which was coupled with alkyne **26**, was readily prepared in 75% overall yield from 4-O-methyl-3,5-dihydroxybenzoic acid, by silylation,¹⁷ LiAlH_4 reduction to the benzyl alcohol,^{1a,f} and chlorination with thionyl chloride. For the coupling of benzyl chloride **27** and alkyne **26**, the Cu-free conditions developed by Buchwald for the Heck alkynylation of benzyl chlorides proved to be the most effective approach.¹⁸ Coupling product **28** was reliably obtained in good yield using $\text{Pd}(\text{OAc})_2$ as the precatalyst and X-Phos as the ligand. DIBAL reduction of the ester followed by Dess–Martin periodinane (DMP) oxidation of the resulting alcohol gave aldehyde **29** in 71% overall yield. Condensation with cyclopropylmethylamine then provided **11**, which was taken on to the next step without purification.

Next, imine **11** was treated with 5 mol% of $[\text{RhCl}(\text{coe})_2]$ precatalyst using $(\text{pNMe}_2)\text{PhPEt}_2$ as the ligand with heating in



Scheme 2 Reactions and conditions: (a) $(\text{COCl})_2$ (1.16 equiv.), DMSO (2.2 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2 , $-78 \rightarrow 23^\circ\text{C}$; (b) $\text{P}(\text{OEt})_3$, neat, 120°C ; (c) $\text{LiOH} \cdot \text{H}_2\text{O}$ (1.1 equiv.), MS 4 Å, THF, reflux; (d) $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (1 mol%), $(\text{DHQD})_2\text{PHAL}$ (5 mol%), $\text{K}_3\text{Fe}(\text{CN})_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), MeSO_2NH_2 (1.00 equiv.), $\text{tBuOH}/\text{H}_2\text{O}$, 0°C ; (e) 2,2-dimethoxypropane (10 equiv.), $\text{TsOH} \cdot \text{H}_2\text{O}$ (10 mol%), CH_2Cl_2 , 0°C ; (f) $\text{Pd}(\text{OAc})_2$ (5 mol%), XPhos (15 mol%), Cs_2CO_3 (1.5 equiv.), dioxane, 65°C ; (g) DIBAL (4.0 equiv.), THF, -78°C ; (h) DMP (1.75 equiv.), pyridine (6.0 equiv.), CH_2Cl_2 , 0°C ; (i) cyclopropylmethylamine (1.2 equiv.), MS 3 Å, PhMe , 23°C .

toluene to initiate the $\text{Rh}(\text{I})$ -catalysed cascade sequence. This process proceeds by $\text{Rh}(\text{I})$ -catalysed C-H activation followed by intramolecular insertion of the alkyne to give azatriene **12**, which *in situ* undergoes rapid electrocyclization to provide 1,2-dihydropyridine **13** (Scheme 3). This cascade process not only forms the desired bicyclic ring system, but also proceeds with high torque-selectivity as enforced by the isopropylidene protected diol to provide the desired diastereomer.¹² Without isolation, hexahydroisoquinoline **13** was reduced under mild



Scheme 3 $\text{Rh}(\text{I})$ C-H functionalization cascade. Condition and reagents: (a) $[\text{RhCl}(\text{coc})_2]$ (5 mol%), $(\text{pNMe}_2)\text{PhPEt}_2$ (10 mol%), PhMe , 85°C ; (b) $\text{NaBH}(\text{OAc})_3$ (5.0 equiv.), AcOH , EtOH , 0°C .



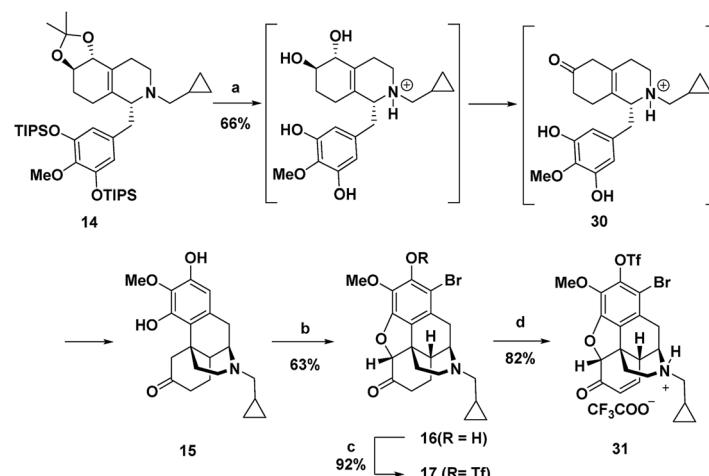
conditions to give the octahydroisoquinoline **14** as a single stereoisomer in 66% overall yield from imine **11**.

Treatment of octahydroisoquinoline **14** with dilute H_3PO_4 and heat afforded morphinan **15** in 66% yield (Scheme 4). Acid treatment to provide morphinan **15** likely proceeds by removal of the silyl and acetonide protecting groups followed by *in situ* redox neutral conversion of the diol to the keto group *via* allylic alcohol ionization and a hydride shift to provide **30**, which then undergoes Grewe cyclization. Methods for α -bromination and subsequent nucleophilic displacement by an adjacent phenol as developed for the synthesis of codeine¹³ gave the dihydrobenzofuran **16** in good overall yield. Two equivalents of Br_2 were needed because the first equivalent of Br_2 was very rapidly consumed by bromination of the highly electron-rich aromatic ring. Bromine substitution did not pose a problem because we anticipated that it could be removed with a global reduction step planned for later in the sequence (*vide infra*). Prior to installation of the C-14 hydroxyl, the free phenol in **16** was converted to the triflate in **17**,¹⁷ which would also be removed in the reduction step.

C-14 C–H hydroxylation of triflate **17** first required dehydrogenation to enone **31** in order to activate this site for γ oxidation (Scheme 4). Direct dehydrogenation has been reported to proceed with low yield for basic opioids with *N*-alkyl amine substituents.¹⁴ To overcome this challenge in the synthesis of opioids, the amine is typically protected as a sulfonamide or carbamate,^{19,20,21,22} which then requires subsequent protecting group removal and installation of the *N*-alkyl group. Alternatively, more indirect, longer sequences have been developed to introduce this unsaturation.¹⁹ We instead chose to investigate contemporary ketone dehydrogenation approaches that have been reported to be compatible with amine functionality. We first evaluated the IBX-MPO system, but the conversion of **17** to enone **31** was not observed.²⁰ Efficient, catalytic dehydrogenation methods utilizing $[Pd(\text{allyl})_2\text{Cl}]_2$ with zinc amide bases have recently been reported,²¹ but only partial conversion to enone **31** along with some allylation at the α -position occurred. Dehydrogenation with $Pd(\text{TFA})_2$ in AcOH using O_2 as an external oxidant resulted in significant *N*-dealkylation.²² This outcome is not

surprising because $Pd(\text{II})$ catalysts under oxidizing conditions have been developed for the *N*-dealkylation of tertiary amines.²³ However, by addition of trifluoroacetic acid to protect the amine as the corresponding salt, along with $DMSO$ as a coordinating solvent to stabilize $Pd(\text{TFA})_2$, complete conversion of ketone **17** was observed, with enone **31** isolated in 82% yield.

For the C-14 C–H hydroxylation of enone **31**, we looked for inspiration in prior semi-syntheses of oxycodone from morphine and codeine. Unfortunately, neither $Co(\text{OAc})_3$ in acetic acid as reported by Rice²⁴ nor MnO_2 in CHCl_3 as reported by Sainsbury²⁵ resulted in C-14 hydroxylation of **31**. We next investigated a method reported for the direct C-14 C–H hydroxylation of codeinone by metal-catalysed peroxidation with O_2 followed by *in situ* reduction with sodium thiosulfate (entry 1, Table 1).²⁶ Disappointingly, no product was detected presumably because enone **31** is completely insoluble in the aqueous pH 8 buffer used as the solvent.²⁷ This led us to extensively explore organic co-solvents in combination with different oxidation catalysts and reductants. A large number of different co-solvents were first investigated, including DMF , THF , EtOH , $DMSO$ and CH_3CN , but little to no product was detected. With pyridine as a 1 : 1 co-solvent with aqueous pH 8 buffer, enone **31** was highly soluble, and while some of the desired C–H hydroxylation product **18** was formed, extensive over-oxidation occurred as determined by LCMS (entry 2). However, by attenuating the basicity of the PBS buffer to pH 7, an improved yield of desired product **18** was obtained (entry 3). Under these conditions, $CuSO_4$ proved to be a superior oxidation catalyst than $KMnO_4$ (entry 4). Use of ketoglutaric acid instead of thiosulfate to reduce the peroxide intermediate was investigated for both $KMnO_4$ (entry 5) and $CuSO_4$ (entry 6). A significant improvement was observed for both catalysts with the highest yield obtained for $CuSO_4$ (entry 6). Finally, varying the ratio of pyridine to PBS buffer resulted in vast differences in reaction rate. While the use of pyridine without any aqueous co-solvent resulted in a slower rate, reaction progress could be more easily monitored and therefore the reaction could be reliably terminated before significant over-oxidation had occurred (entry 7).



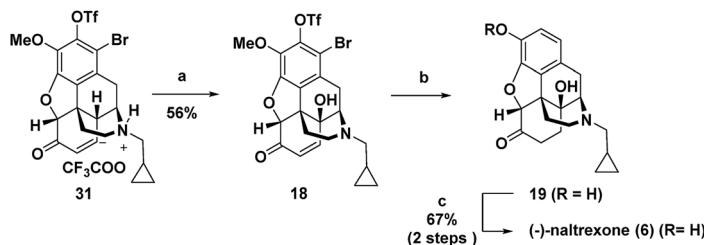
Scheme 4 Synthesis of dehydrogenated enone **31** as the precursor to Installation of C-14. Conditions and reagents: (a) 55% H_3PO_4 , 125 °C; (b) Br_2 (2.0 equiv.), AcOH , 23 °C; $NaOH_{(\text{aq})}$, 23 °C; (c) Tf_2O (3.3 equiv.), pyridine, 0 °C; (d) $Pd(\text{TFA})_2$ (1.4 equiv.), TFA , $DMSO$, 80 °C.



Table 1 Optimization of γ -C–H hydroxylation of 31

Entry	Catalyst ^a (2 mol%)	Reductant ^b (4.5 equiv.)	Solvent ^c	Time ^d (h)	NMR yield ^e (%)	
					sm(31)	pdt(18)
1	KMnO ₄	Na ₂ S ₂ O ₃	PBS pH 8	42	49	0
2	KMnO ₄	Na ₂ S ₂ O ₃	PBS pH 8/pyridine (1 : 1)	42	0	11
3	KMnO ₄	Na ₂ S ₂ O ₃	PBS pH 7/pyridine (1 : 1)	42	11	17
4	CuSO ₄	Na ₂ S ₂ O ₃	PBS pH 7/pyridine (1 : 1)	5	5	31
5	KMnO ₄	Ketoglutaric acid	PBS pH 7/pyridine (1 : 1)	18	15	33
6	CuSO ₄	Ketoglutaric acid	PBS pH 7/pyridine (1 : 1)	1.5	0	55
7	CuSO ₄	Ketoglutaric acid	Pyridine	48	8	59

^a Catalysts were added as 5 mM stock solutions in deionized H₂O. ^b Reductants were added as a 150 mM stock solution in deionized H₂O. ^c All solvents were sparged with O₂ prior to reaction. ^d The reaction was stopped when the product was at maximum yield as determined by LCMS exact ion count. ^e 1,3,5-Trimethoxybenzene was used as a standard for NMR yields. Remaining percent balance corresponds to unidentified overoxidized or degraded product.



Scheme 5 Installation of C-14 hydroxylation and endgame synthesis to (–)-naltrexone (6). Conditions and reagents: (a) CuSO₄ (2 mol%), ketoglutarate (4.5 equiv.), pyridine, 23 °C, O₂; (b) Et₃N (10 equiv.), Pd(OH)₂ (20 wt%), EtOAc : MeOH = 1 : 3, H₂, 23 °C; (c) BBr₃ (5 equiv.), CH₂Cl₂, –40 → 0 °C.

After γ -hydroxylation to afford 18, we attempted to remove the aryl bromide and triflate as well as hydrogenate the enone to access 19 in a single step (Scheme 5). While formic acid with Pd(PPh₃)₄ only reductively cleaved the triflate and bromide, hydrogenation with H₂ and Pd/C reduced the double bond and achieved hydrodebromination but without reductive cleavage of the triflate. However, Pearlman's catalyst (Pd(OH)₂) under 1 atm of H₂ resulted in the complete reduction of the double bond along with the reductive removal of both the bromide and the triflate to give 19 in nearly quantitative yield.²⁸ For this reason, 19 was not purified but rather was directly submitted to final BBr₃ mediated demethylation, affording (–)-naltrexone 6 in 67% yield over the two steps.

Conclusions

We have developed a new approach for the synthesis of (–)-naltrexone in 17 linear steps. Starting with commercially available achiral substrates, a bicyclic hexahydroquinoline intermediate was accessed *via* a Rh(I)-catalyzed C–H alkenylation

and torquoselective electrocyclization cascade. Grewe cyclization then provided the morphinan core with a concomitant hydride shift introducing the C-6 oxo functionality present in naltrexone. After formation of the dihydrobenzofuran, Pd-mediated dehydrogenation to the enone followed by allylic C–H oxidation using Cu(II) and O₂ introduced the C-14 hydroxyl group. This new route for the asymmetric synthesis of (–)-naltrexone from simple, achiral precursors could provide a means to prepare morphinan derivatives that would be difficult to access through semi-synthesis from opioid natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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