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Synthesis of (−)-Morphine: Application of Sequential Claisen/Claisen Rearrangement of an Allylic Vicinal Diol

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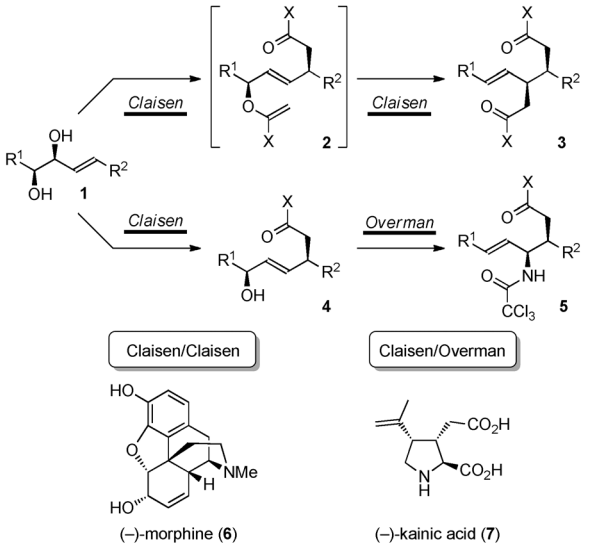
Abstract: A detailed exploration of the synthesis of (−)-morphine based on sequential [3,3]-sigmatropic rearrangements is described. The sequential Claisen/Claisen rearrangements of an allylic vicinal diol resulted in the stereoselective formation of the two contiguous carbon centers, including a sterically encumbered quaternary carbon, in a single operation. The two ethyl esters generated in this reaction were successfully differentiated during a subsequent Friedel–Crafts-type cyclization. The (−)-morphine double bond was introduced at a late stage in our first-generation synthesis, but was formed at an earlier stage in the second-generation synthesis, resulting in a more efficient route to the end product.

Keywords: allylic compounds · chirality · morphine · sigmatropic rearrangement · total synthesis

Introduction

Our laboratory is engaged in a program devoted to the development of sequential [3,3]-sigmatropic rearrangements of allylic vicinal diols **1** with applications in the total synthesis of complex natural products (Scheme 1).[1] Whereas the [3,3]-sigmatropic rearrangement of simple allylic alcohols has been recognized as a well-defined method in organic synthesis, the reactions derived from allylic vicinal diols such as **1** are still undeveloped in spite of their potential utility. Allylic vicinal diols can undergo two sigmatropic rearrangements in a sequential manner. In this process, the first rearrangement results in new carbon–carbon or carbon–heteroatom bond, accompanied by regeneration of a new allylic alcohol, which undergoes the second rearrangement. Based on this concept, we have succeeded in developing a method consisting of two sequential sigmatropic rearrangements utilizing the Claisen rearrangement.[2–4] The Claisen/Claisen rearrangement of **1** forms two functional groups in a one-pot reaction (**1**→**2**→**3**), whereas the Claisen/Overman rearrangement introduces two different functional groups from the same initial allylic diol (**1**→**4**→**5**). This Claisen/Overman rearrangement technique was successfully applied to the total synthesis of (−)-kainic acid (**7**).[2]

To demonstrate the practical utility of the sequential Claisen/Claisen rearrangement, we chose the synthesis of the well-known principal alkaloid (−)-morphine (**6**), isolated from the opium poppy, *Papaver Somniferum*.[5] This opiate has been used as an efficient analgesic and anaesthetic for a long time, despite its potentially serious addictive side effects. Structurally, (−)-morphine includes a strained pentacyclic core with five contiguous chiral centers, one of which is a benzylic quaternary carbon. The important biological activity of this compound, as well as its challenging structure, have resulted in continuous interest within the synthetic organic community.[6,7] In this paper, we report the full details of a formal synthesis of (−)-morphine using the sequential Claisen/Claisen rearrangement of an allylic vicinal diol.



Scheme 1. Sequential Claisen/Claisen rearrangement and Claisen/Overman rearrangement applied to the total synthesis of natural products.

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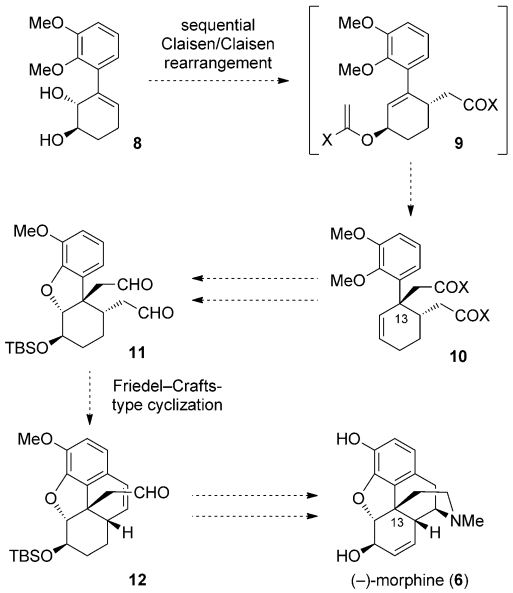
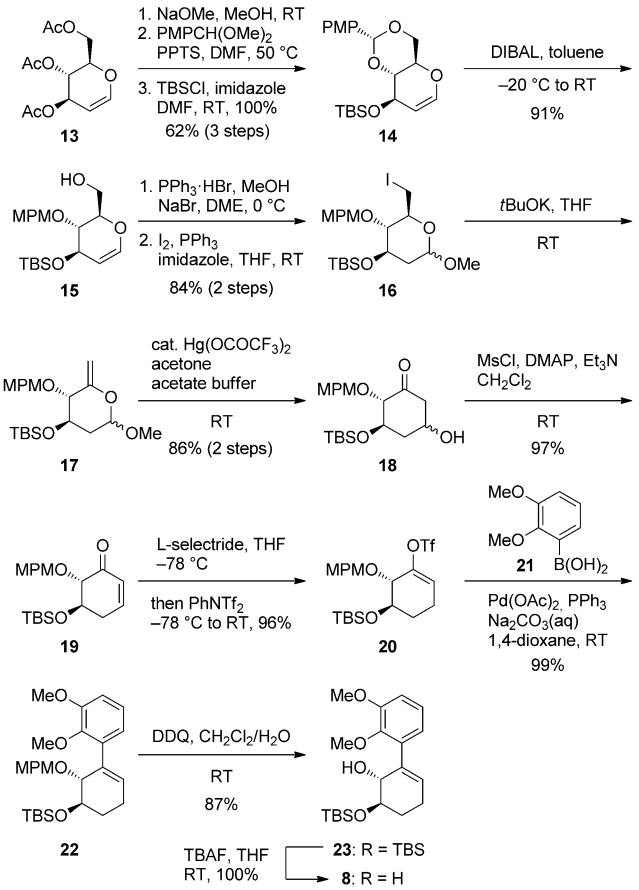
Results and Discussion

Our central strategy for the total synthesis of (−)-morphine was based on the sequential Claisen/Claisen rearrangement of an allylic vicinal diol **8** (Scheme 2). The first Claisen rearrangement of **8** would give **9**, which would spontaneously undergo the second Claisen rearrangement. This reaction sequence would establish two contiguous stereocenters, including the highly congested C13-quaternary center. The stereochemical outcomes of **10** are completely dependent on the stereochemistry of diol **8**, which is derived from the two secondary alcohols of D-glucal (Scheme 2). To succeed in this synthetic strategy, differentiation between the two identical functional groups resulting from the sequential rearrangement was critical. We therefore considered the use of a new Friedel–Crafts-type reaction of bis-aldehyde **11** (Scheme 2).[8] In this reaction, only the spatially proximal aldehyde group to the aromatic ring would undergo cyclization to give the tetracyclic system **12**, which would be an appropriate intermediate for the total synthesis of (−)-morphine (**6**).



Scheme 2. Synthetic plan for the total synthesis of (−)-morphine (**6**).

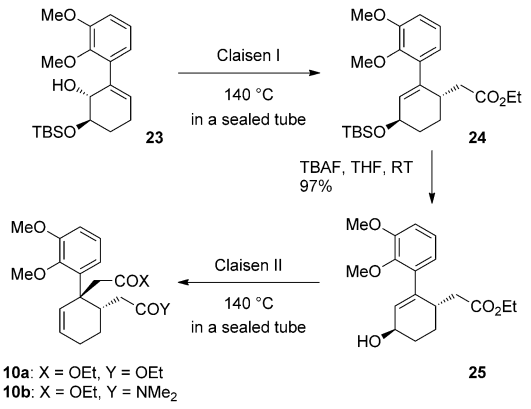
As shown in Scheme 3, the allylic vicinal diol **8** was prepared by taking advantage of the D-glucal scaffold through Ferrier's carbocyclization.[9] Deacetylation of tri-*O*-acetyl-D-glucal (**13**) with sodium methoxide provided the D-glucal, which was converted to the *p*-anisylidene derivative. The remaining secondary alcohol was protected as a TBS ether to give the known compound **14**.[10] The regioselective cleavage of anisylidene acetal **14** with diisobutylaluminium hydride (DIBAL) at −20 °C afforded primary alcohol **15**. The glucal was then converted to the methyl glycoside by treatment of **15** with PPh_3·HBr and MeOH in DME,[11] followed by iodination of the primary alcohol to give **16** in 84% yield (2 steps). Elimination of **16** with *t*BuOK then gave 5-enopyranoside **17**. Exposure of **17** to a catalytic amount of $Hg(OCOCF_3)_2$ in acetone/acetate buffer efficiently initiated the Ferrier's carbocyclization, followed by β elimination through the mesylate to give cyclohexenone derivative **19** in 83% yield (3 steps). The 1,4-reduction of **19** with L-Selectride, followed by subsequent in situ-trapping with $PhNTf_2$ provided enol triflate **20**.[12] Suzuki–Miyaura coupling of **20** with 2,3-dimethoxyphenylboronic acid (**21**) proceeded smoothly at 99% yield despite the steric congestion.[13] The removal of the 4-methoxybenzyl (MPM) and *tert*-butyl dimethylsilyl (TBS) groups afforded the key intermediate **8**.



Scheme 3. Synthesis of allylic vicinal diol **8**. PMP = *p*-methoxyphenyl, PPTS = pyridinium *p*-toluenesulfonate, Ms = methane sulfonyl, DMAP = 4-dimethylaminopyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Although our goal was the development of the sequential Claisen/Claisen rearrangement as a one-pot process, we first investigated a stepwise double Claisen rearrangement.[14] The Johnson-type Claisen rearrangement of allylic alcohol **23** with propionic acid in the presence of molecular sieves (MS, 4 Å) gave **24** in 87% yield (Table 1, entry 1). After the removal of the TBS group with tetrabutylammonium fluoride (TBAF), the resulting allylic alcohol **25** was subjected to the second Johnson-type Claisen rearrangement with propionic acid, giving **10a** with a quaternary carbon center in 44% yield. The yield of the first rearrangement was low

Table 1. Results of stepwise double Claisen rearrangements.[a]



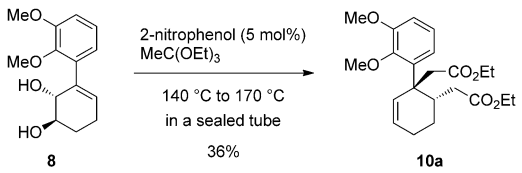
Entry	Claisen I	Claisen II	Yield [%][b] 24	10
1	$MeC(OEt)_3$, $EtCO_2H$, MS (4 Å)	$MeC(OEt)_3$, $EtCO_2H$	87	**10a**: 44
2	$MeC(OEt)_3$, 2-nitrophenol	$MeC(OEt)_3$, $EtCO_2H$	53	**10a**: 44
3	$MeC(OEt)_3$, $EtCO_2H$, MS (4 Å)	$MeC(OEt)_3$, 2-nitrophenol	87	**10a**: 57
4	$MeC(OEt)_3$, $EtCO_2H$, MS (4 Å)	$MeC(OEt)_2NMe_2$, *o*-xylene	87	**10b**: 90

[a] Claisen I: Compound **23**, acid (0.4 equiv), MS (4 Å), $MeC(OEt)_3$, 140 °C in a sealed tube; Claisen II: Compound **25**, acid (5 mol %), $MeC(OEt)_3$, 140 °C in a sealed tube. [b] Yield of the isolated product after purification by column chromatography on silica gel.

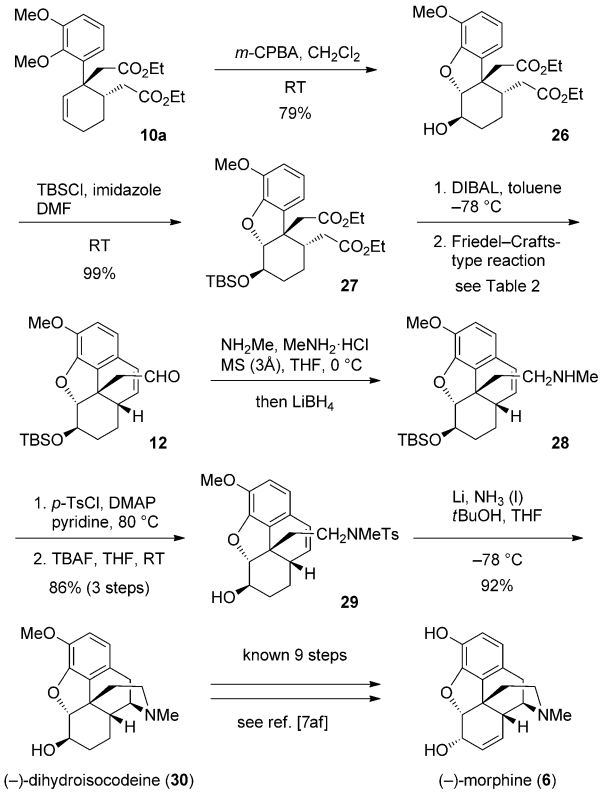
when the less acidic 2-nitrophenol was employed (Table 1, entry 2). On the other hand, the second Claisen rearrangement was more efficient when 2-nitrophenol was used, providing **10a** in 57 % yield (Table 1, entry 3).[15] The moderate yields of the second rearrangement were mainly due to decomposition of the substrates, probably through the formation of stabilized conjugated carbocations. The use of an Eschenmoser-type reaction for the second rearrangement proved to be the best conditions giving **10b** in 90 % yield (Table 1, entry 4). Although the combination of Johnson and Eschenmoser-type rearrangements created optimal conditions in terms of the yield of the stepwise double Claisen rearrangement itself, the further transformation of dimethyl amide **10b** turned out to be troublesome due to its inertness. Thus, we concluded the most appropriate intermediate for the total synthesis was bis-ethylester **10a** as synthesized by the Johnson-type reaction.

With the two contiguous carbon centers thus established in a stepwise fashion, we turned our attention to the cascade version of this portion of the synthesis (Scheme 4). Treatment of allylic vicinal diol **8** with $MeC(OEt)_3$ in the presence of 2-nitrophenol at 140 to 170 °C in a sealed tube initiated the sequential Claisen/Claisen rearrangement in 36 % yield.[16] Although the yield was moderate, likely because the most optimal acid may not have been used as suggested by Table 1, it is noteworthy that the vicinal tertiary and quaternary carbons required for the subsequent synthesis of (−)-morphine were stereoselectively created in a single operation.

Having successfully developed the sequential Claisen/Claisen rearrangement, we next attempted the construction of the dihydrobenzofuran moiety (Scheme 5). Treatment of **10a** with *meta*-chloroperbenzoic acid (*m*-CPBA) induced demethylating etherification through the epoxide to give **26** in 79 % yield.[7t] The resulting alcohol was protected as a TBS ether. The stage was now set for the crucial Friedel–Crafts-type reaction (Table 2). After the partial reduction of bis-ester **27** with DIBAL, the crude bis-aldehyde was immediately subjected to the next Friedel–Crafts type reaction without further purification, since the bis-aldehyde is prone to hydrate formation. Whereas treatment with aqueous toluene sulfonic acid (*p*-TsOH·H_2O) in benzene at 80 °C resulted in decomposition of the reacting species (Table 2, entry 1), the reaction with camphorsulfonic acid (CSA) gave phenan-

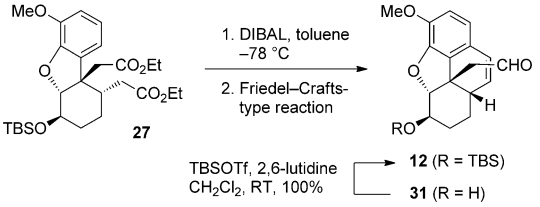


Scheme 4. Sequential Claisen/Claisen rearrangement of allylic vicinal diol **8**.



Scheme 5. First-generation synthesis of (−)-morphine (**6**).

Table 2. Differentiation of the two ethyl esters through a Friedel–Crafts-type cyclization.



Entry	Conditions	Yield [%][a]	
		12	**31**
1	*p*-TsOH·H_2O, PhH, 80 °C	0	0
2	CSA, PhH, 80 °C	24	0
3	CSA, 1,2-dichlorobenzene, 80 °C	0	0
4	CSA, $(CH_2Cl)_2$, 80 °C	32	0
5	CSA, $(CH_2Cl)_2$, RT	37	0
6	montmorillonite K-10, $(CH_2Cl)_2$, RT	38	43

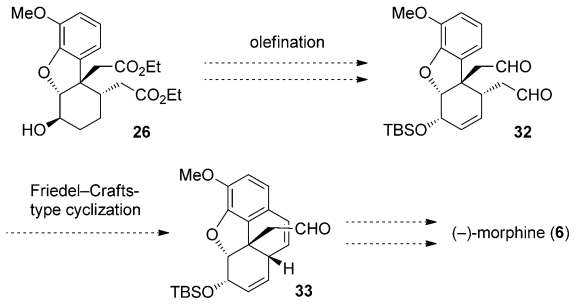
[a] Yield of the isolated product after purification by column chromatography on silica gel.

throfuran **12** in 24% yield (Table 2, entry 2). As we anticipated, the proximal aldehyde to the aromatic ring selectively underwent cyclization. The nature of the solvent employed also had effects on the yield. The best results were obtained with dichloroethane, resulting in 32% yield (Table 2, entries 2–4). Because prolonged reaction times at 80 °C led to the decomposition of **12**, we subsequently lowered the reaction temperature, resulting in a slight improvement (Table 2, entry 5). We ultimately found that the utilization of montmorillonite K-10 at room temperature significantly improved the reaction efficiency, giving **12** in 38% yield, along with the free alcohol **31** in 43% yield, which was readily converted to **12** (Table 2, entry 6).[17] Thus, we successfully developed the new Friedel–Crafts-type cyclization.

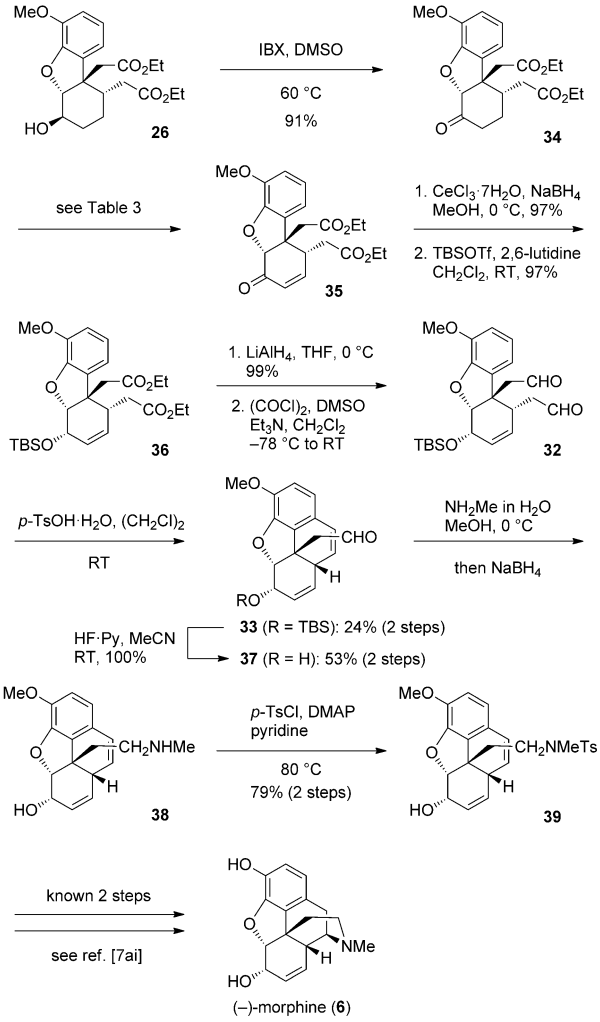
The one remaining challenge for the total synthesis of (−)-morphine (**6**) was the formation of the piperidine ring (Scheme 5). The reductive amination of **12** with methyl amine, followed by N-tosylation and TBS-deprotection gave **29** (a known intermediate reported by Parker) in 86% yield (3 steps).[7af] Finally, synthesis of (−)-dihydroisocodeine (**30**) was achieved under Birch conditions by using Li/NH_3 in the presence of *t*BuOH, resulting in the first-generation formal synthesis of (−)-morphine.[7af]

Although we succeeded in developing the first-generation synthesis of (−)-morphine (**6**), (−)-dihydroisocodeine (**30**) still required several reaction steps to complete the total synthesis of (−)-morphine, primarily due to the requirement for olefination. We reasoned that, if the double bond in the cyclohexene ring could be introduced at an earlier stage, the synthetic route would become more efficient (Scheme 6, **26**→**32**). Our major concern in this respect was that the Friedel–Crafts-type reaction under acidic conditions (**32**→**33**) might lead to decomposition due to the labile allylic TBS ether in **32**.

The second-generation synthesis commenced with the 2-iodoxybenzoic acid (IBX)-oxidation of **26** at 60 °C (Scheme 7).[18] As shown in Table 3, the subsequent olefination of ketone **34** was not trivial. Treatment with PhSeCl under basic conditions by using $NaN(TMS)_2$, followed by oxidative elimination with $NaIO_4$ provided the enone **35** in 34% yield over two steps (Table 3, entry 1). Under acidic conditions this reaction produced a similar result (Table 3, entry 2).[19] Employing the more reactive PhSeOTf resulted

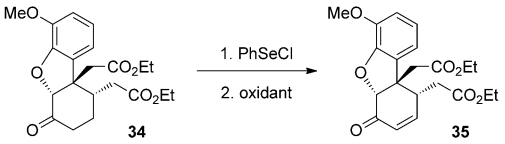


Scheme 6. New synthetic plan toward the total synthesis of (−)-morphine (**6**).



Scheme 7. Second-generation synthesis of (−)-morphine (**6**).

Table 3. Results for insertion of a double bond through selenylation.



Entry	Selenylation	Elimination	Yield [%][a]
1	PhSeCl, $NaN(TMS)_2$, THF, RT	$NaIO_4$, THF/H_2O, RT	34
2	PhSeCl, conc. HCl, EtOAc, RT	$NaIO_4$, THF/H_2O, RT	36
3	PhSeCl, AgOTf, EtOAc, RT	$NaIO_4$, THF/H_2O, RT	27
4	PhSeCl, AgOTf, BF_3·Et_2O, EtOAc, RT	$NaIO_4$, THF/H_2O, RT	47
5	PhSeCl, AgOTf, BF_3·Et_2O, EtOAc, RT	Davis Reagent, $CHCl_3$, RT	60

[a] Yield of isolated product after purification by column chromatography on silica gel.

in decreased yield (Table 3, entry 3). After the extensive investigation, we eventually determined that the addition of BF_3·Et_2O[20] to PhSeOTf optimized the conditions of the selenylation step (Table 3, entries 3 and 4). The oxidative elimination step was improved with the use of Davis reagent,[21] giving enone **35** in 60% yield over 2 steps (Table 3, entry 5).

With enone **35** in hand, we turned our attention to the Friedel–Crafts-type cyclization (Scheme 7). A stereoselective 1,2-reduction of **35** under Luche's conditions[22] gave the β-alcohol, which was protected as a TBS ether to give **36** in 94% (2 steps). Bis-aldehyde **32** was then prepared through a two-step sequence including $LiAlH_4$-reduction and Swern oxidation.[23] The crude aldehyde **32** was immediately subjected to the next Friedel–Crafts reaction. As we had feared, the reaction of bis-aldehyde **32** containing the acidic labile allylic TBS-ether led to significant decomposition with montmorillonite K-10. Extensive screening, however, revealed that the utilization of *p*-TsOH·H_2O at room temperature induced both cyclization and the removal of the TBS group simultaneously, giving phenanthrofuran **33** in 53% yield, along with undeprotected product **37** in 24% yield, which was converted to **33** with HF·Py in MeCN. The reductive amination of **33**[7ad, ae] and subsequent N-tosylation afforded Guillou's intermediate **39**.[7ai] Our synthetic sample was indistinguishable from their spectral data based on ^1H and ^{13}C NMR spectroscopy, HRMS, and IR. It is known that **39** can be converted into (−)-morphine through two further reaction steps, therefore we have accomplished the second-generation synthesis of (−)-morphine (**6**).

Conclusion

We have demonstrated the formal synthesis of (−)-morphine based on a new strategy by using a [3,3]-sigmatropic rearrangement. The sequential Claisen/Claisen rearrangement of an allylic vicinal diol resulted in the formation of two contiguous stereocenters, including a benzylic quaternary carbon, in a single step. The two ester groups generated in the rearrangment were successfully differentiated during the subsequent Friedel–Crafts type cyclization to give the phenanthrofuran structure. Whereas our first-generation synthesis required the troublesome introduction of the key double bond at a late stage in the process, the second-generation synthesis introduced the double bond much sooner, resulting in a more efficient synthesis. In addition, the Friedel–Crafts type cyclization used in the second-generation synthesis showed this reaction to be highly effective even in the presence of an acidic labile functional group.

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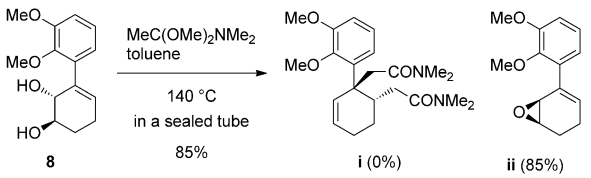

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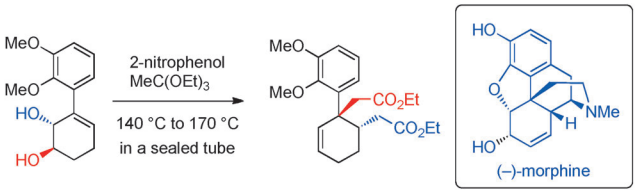

Pain-free synthesis! The sequential sigmatropic rearrangements of allylic vicinal diols offer a practical process for the synthesis of structurally complex chiral compounds. The synthesis of (−)-morphine was achieved by employing a sequential Claisen/Claisen rearrangement as a key step (see scheme). The reaction of an allylic vicinal diol was employed to introduce a vicinal tertiary and quaternary carbon centers, and the resulting bis-ester was differentiated in a subsequent Friedel–Crafts-type cyclization.

Total Synthesis

*M. Ichiki, H. Tanimoto, S. Miwa, R. Saito, T. Sato, N. Chida** ▮▮▮▮–▮▮▮▮

Synthesis of (−)-Morphine: Application of Sequential Claisen/Claisen Rearrangement of an Allylic Vicinal Diol