Tetrahedron Letters 53 (2012) 5660–5662

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of (±)-monomorine

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ARTICLE INFO

Article history:
Received 12 July 2012
Revised 7 August 2012
Accepted 9 August 2012
Available online 16 August 2012

Keywords:
Hydrogenation
Claisen-Schmidt
Monomorine

ABSTRACT

An efficient, two-operation synthesis of the trail ant pheromone (±)-monomorine is reported. The synthesis features an aqueous Claisen-Schmidt condensation followed by the stereocontrolled installation of the three resident stereocenters in a single operation.

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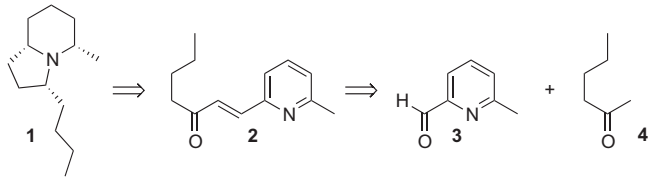
The natural product (+)-monomorine[1] (**1**) continues to generate substantial interest within the synthetic community. The synthesis of this pheromone, either as the naturally-occurring enantiomer,[2–4] its antipode,[5,6] both enantiomers,[7] or the racemic mixture,[8,9] remains a popular proving ground for the development and exemplification of new synthetic methodology. Our interest in this molecule arises from its compact, stereochemically rich structure. We hypothesized that a highly efficient[10] synthesis could be realized using a functionalized pyridine starting material, an atom economical[11] carbon–carbon bond forming reaction, and attention to green chemistry principles.[12,13]

Retrosynthetic analysis of **1** suggested the hydrogenation of a pyridine moiety as the source of piperidine in **1** (Scheme 1). Previous syntheses of monomorine demonstrated that a highly stereoselective process to establish the 2,6-*cis* stereochemistry would be feasible.[14,15] Moreover, we believed that the pyrrolidine ring could also be installed stereoselectively in the same reaction vessel by the intramolecular reductive amination of an appropriately placed ketone. Our confidence in this approach was bolstered by Yamaguchi's observations of high stereoselectivity in his early synthesis of racemic monomorine.[16,17] Given the ease of formation of conjugated enone systems and the susceptibility of the alkene to hydrogenation, α,β-unsaturated ketone **2** presented itself as an ideal synthetic precursor. Provided that acceptable levels of regioselectivity could be achieved, a Claisen-Schmidt condensation using commercially available 6-methylpyridine-2-carbaldehyde (**3**) and 2-hexanone (**4**) would provide expedient and atom-economical[11] access to this key intermediate.

Our exploration of the Claisen-Schmidt reaction began by adapting conditions reported by Sinisterra and coworkers using a partially dehydrated barium hydroxide catalyst (C-200) in Claisen-Schmidt condensations.[19] The use of commercially available $Ba(OH)_2 \cdot H_2O$ as the promoter in refluxing ethanol solvent afforded a very modest yield (entry 1, Table 1) of the desired ketone **2**. The reaction was complicated by the formation of several byproducts (Scheme 2), including the aldol adduct **5** (ca 16%) and primary alcohol **7** (ca. 12%), as well as β-ethoxyketone **6** and several unidentified impurities in smaller amounts. Alcohol **7** is presumably formed via a Cannizzaro reaction.

Moreover, the reaction mixture was highly heterogeneous, rendering efficient stirring difficult. The multiple byproducts, as well as this heterogeneity, led us to consider alternative conditions.

Recent years have seen an increasing recognition of the value of water as a solvent for organic reactions.[12,13,20–23] We believed that water would be the ideal solvent for overcoming issues with the precipitation of inorganic solids and opted to explore its use as a solvent. We were pleased to find that this small change in conditions resulted in an improved yield of 56% (entry 2, Table 1). Gratifyingly as well, the reaction appeared to be highly regioselective, as we did not observe the regioisomeric adduct by ^{1}H NMR analysis



Scheme 1. Retrosynthetic analysis.[18]

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http://dx.doi.org/10.1016/j.tetlet.2012.08.041

Table 1
Optimization of Claisen-Schmidt conditions for synthesis of ketone 2[a]

Entry	Equiv ketone	Base (equiv)	% yield
1[b]	2	$Ba(OH)_2{\cdot}H_2O$ (0.2)	28
2	2	$Ba(OH)_2{\cdot}H_2O$ (0.2)	56
3[c]	2	$Ba(OH)_2{\cdot}H_2O$ (0.2)	0
4	4	$Ba(OH)_2{\cdot}H_2O$ (0.2)	63
5	1.2	$Ba(OH)_2{\cdot}H_2O$ (0.2)	37
6[d]	4	$Ba(OH)_2{\cdot}H_2O$ (0.2)	63
7	1.2	$Ba(OH)_2{\cdot}H_2O$ (0.04)	51
8	5	$Ba(OH)_2{\cdot}H_2O$ (0.04)	52
9	4	NaOH (0.2)	74
10	2	KOH (0.2)	66
11	2	NaOH (0.2)	71
12	1.1	NaOH (0.2)	66
13[e]	2	NaOH (0.2)	82

[a] General conditions: The reagents were combined in the proportions described and heated at reflux in water for 45 min. Yields reported are after purification by flash chromatography (heptane:ethyl acetate as eluent).
[b] Reaction conducted in refluxing ethanol.
[c] Reaction conducted in the absence of solvent.
[d] Dropwise addition of **3** as a solution in water.
[e] A solution of NaOH in water was used in place of solid NaOH.

of the crude reaction mixture. Notably, no reaction took place in the absence of water (entry 3).

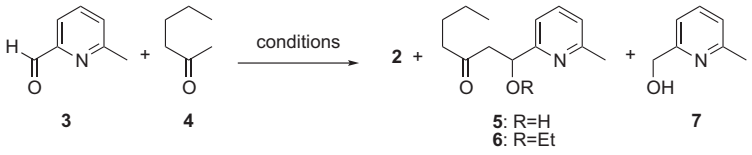
The major observed byproduct was alcohol **7**. We speculated that increasing the equivalents of ketone would help to overcome the Cannizzaro reaction. The use of 4 equiv ketone indeed improved the yield slightly (entry 4), while decreasing the ketone to 1.2 equiv substantially reduced the yield (entry 5). Dropwise addition of a solution of aldehyde **3** in water provided no advantage (entry 6). Since the Cannizzaro side reaction is stoichiometric in hydroxide, we also explored the use of less base. Using only 4 mol% $Ba(OH)_2{\cdot}H_2O$, a fair yield was achieved with either 1.2 or 5 equiv ketone (entries 7 and 8). Incomplete elimination of the hydroxyketone intermediate (**5**) was at least partially responsible for the modest yield in these cases.

Despite these improvements, the overall yield was still suboptimal. We next explored the use of other readily available hydroxide bases, most notably sodium hydroxide.[24] NaOH proved superior to $Ba(OH)_2{\cdot}H_2O$ (entry 9 versus entry 4, Table 1). With NaOH, reducing the amount of ketone to 2 or even 1.1 equiv met with reasonable results (entries 11 and 12) and appeared slightly better than KOH (entry 11 versus 10). Consideration of all of our results led us to use 2 equiv of ketone as the optimal balance between yield and atom economy. Finally, we found that pre-dissolving the base in water before adding it to the reaction medium also had a beneficial effect. Using 2 equiv of the ketone in conjunction with 0.2 equiv NaOH afforded a yield of 82% (entry 13). This reaction was also conducted on multi-gram scale with no loss of yield.[25]

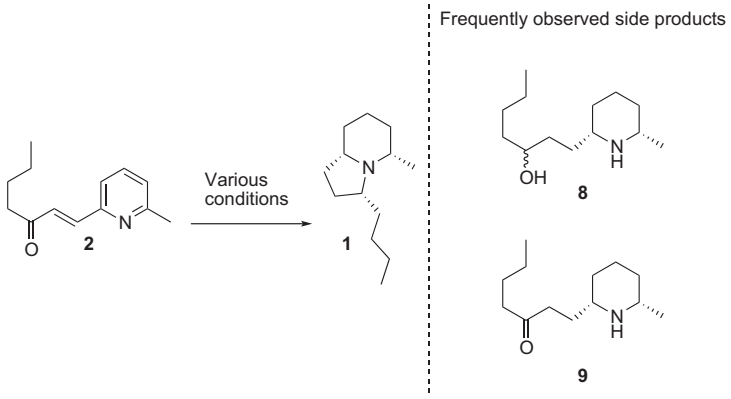
With an efficient and scalable synthesis of ketone **2** in hand, we turned our attention to the alkene reduction/pyridine reduction/reductive amination sequence. Initially, we explored the use of Adam's catalyst[14] and were delighted to observe evidence of the natural product from our first attempt (data not shown). Unfortunately, these conditions proved somewhat capricious and also routinely led to competitive and unproductive reduction of the ketone to a secondary alcohol (**8**, Scheme 3).

We qualitatively screened a number of potential alterative catalysts (Pd/C, Pt/C, Rh/C, and Raney Ni) using an H-Cube™ apparatus. In this exercise, Rh/C[18] was found to be particularly effective at reducing the pyridine ring of **2**, so we chose to examine its use further. Reduction of **2** under strongly acidic conditions (1% HCl in MeOH) led to chemoselective reduction of the pyridine in the presence of the ketone but did not permit the reductive amination, resulting instead in the formation of ketone **9** (Scheme 3). Compound **9** could be converted to (±)-monomorine via a subsequent reductive amination using either H_2 in the presence of PtO_2 or sodium triacetoxyborohydride. Notably, the use of PtO_2 still resulted in competitive reduction of the ketone to form **8** alongside the desired product.

We reasoned that strongly acidic conditions with Rh/C catalysis might hinder the reductive amination by preventing access to the unprotonated secondary amine. Gratifyingly, the use of the milder glacial acetic acid as solvent resulted in the formation of **1** as the major product, with a lesser amount of ketone overreduction. Additional optimization led to the use of 3:1 MeOH:acetic acid as a solvent mixture.



Scheme 2. Initial Claisen-Schmidt condensation of 3 and 4 in ethanol.



Scheme 3. Reduction/reductive amination results.

Table 2
Optimization of one-pot synthesis of monomorine from enone 2[a]

Entry	Catalyst	Ratio **1**:**8**	% yield[b]
1	5% Rh/alumina[c]	60:40	ND
2	5% Rh/C[d]	80:20	ND
3	4.5% Pd/C:0.5% Rh/C[e]	75:25	ND
4	4.5% Pd/C:0.5% Rh/C[f]	80:20	ND
5[g]	5% Rh/alumina[c]	70:30	ND
6[h]	5% Rh/C[d]	ND	52

[a] General conditions: Reactions were carried out on 50 mg **2** using an Endeavor™ catalyst screening system under ca. 45 psi H_2 in 2 mL volume of 3:1 methanol: acetic acid unless otherwise noted.
[b] Isolated yield after flash chromatography; ND = not determined.
[c] Aldrich.
[d] Johnson Mathey (JM) #34.
[e] JM #20.
[f] JM #21.
[g] Reaction was run in 1:1 methanol: trimethylorthoformate as solvent.
[h] 300 mg **2** were used, and a Parr shaker was used to conduct the reaction (45 psi H_2).

Using these conditions, we undertook the final optimization of the conversion of **2** to **1** using a variety of Rh-based catalysts (Table 2). We consistently observed the formation of alcohol **8** as the principal byproduct. By conducting the hydrogenation at 50 °C using commercially available 5% Rh/C as catalyst, we were able to achieve an 80:20 ratio of **1**:**8** (entry 2). Using this methodology, we obtained a 52% yield of the desired product on 300 mg scale (entry 6).[26] ^{1}H and ^{13}C NMR spectra were consistent with the literature values,[7] and a series of NMR experiments (COSY, HSQC, HMBC, NOESY, ROESY, HSQC-TOCSY) also confirmed the relative stereochemistry (see Supplemental data).

By using an atom-economical aqueous Claisen-Schmidt condensation and a stereoselective triple-reduction sequence, we have developed a highly efficient synthesis of racemic monomorine (**1**) in two operations from commercially available aldehyde **3**. Related approaches may also prove useful to the synthesis of other indolizidine natural products.[27]

Acknowledgments

The authors wish to thank the Pfizer summer internship program for support (T.L.). The authors would particularly like to acknowledge Andrew Butler for support in 2D NMR experiments and analysis. Patrick Mullins is recognized for his diligence in byproduct identification. Thuy Hoang is gratefully acknowledged for experimental assistance, as are Drs. Matthew Brown and Tarek Sammakia for helpful discussions.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for compounds **1** and **2**. COSY, HSQC, HMBC, NOESY, ROESY, and HSQC-TOCSY spectra for compound **1**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.041.

References and Notes

1. Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Verwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530.
2. Kim, G.; Jung, S-d; Lee, E-j; Kim, N *J. Org. Chem.* **2003**, *68*, 5395.
3. Davis, F. A.; Zhang, J.; Wu, Y. *Tetrahedron Lett.* **2011**, *52*, 2054.
4. Reddy, C. R.; Latha, B. *Tetrahedron Asymm.* **2011**, *22*, 1849.
5. Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133.
6. Reddy, C. R.; Latha, B.; Rao, N. N. *Tetrahedron* **2012**, *68*, 145.
7. Toyooka, N.; Zhou, D.; Nemoto, H. *J. Org. Chem.* **2008**, *73*, 4575.
8. Lapointe, G.; Schenk, K.; Renaud, P. *Chem. Eur. J.* **2011**, *17*, 3207.
9. Iska, V. B. R.; Verdolino, V.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 1325.
10. Gaich, T.; Baran, P. *J. Org. Chem.* **2010**, *75*, 4657.
11. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
12. Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.
13. Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
14. Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 2662.
15. Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289.
16. Yamaguchi, R.; Hata, E-i; Matsuki, T; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094.
17. Other authors have also confirmed the high stereoselectivity in this transformation. See: (a) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919; (b) Ref.4; For a related stereoselective reductive amination in the synthesis of (+)-trifluoromethyl monomorine, see: (c) Kim, G.; Kim, N. *Tetrahedron Lett.* **2005**, *46*, 423.
18. In this context, it should be noted that a similar approach to a series of octahydroindolizine analgesics has been reported in the patent literature. See: Carmosin, R. J.; Carson, J. R. U.S. Patent 4,582,836, April 15, 1986.
19. Sinisterra, J. V.; Garcia-Raso, A.; Cabello, J. A.; Marinas, J. M. *Synthesis* **1984**, 502.
20. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.
21. Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
22. Wang, Y.; Ye, J.; Liang, X. *Adv. Synth. Catal.* **2007**, *349*, 1033.
23. Mohrig, J. R.; Hammond, C. N.; Schatz, P. F.; Davidson, T. A. *J. Chem. Educ.* **2009**, *86*, 234.
24. Ref.18 also made use of NaOH as a base but utilized methanol as a solvent, stoichiometric amounts of base, reduced temperatures, and acetophenone derivatives as the ketone partner.
25. *(E)-1-(6-methylpyridin-2-yl)hept-1-en-3-one (2):* 6-methylpyridine-2-carbaldehyde (3.00 g, 24.8 mmol, 1.0 equiv) and 2-hexanone (4.86 g, 48.5 mmol, 2.0 equiv) were combined and stirred until the aldehyde dissolved fully. A solution of sodium hydroxide (0.200 g, 5.0 mmol, 0.20 equiv) in water (20 mL) was then added and the resulting mixture heated at reflux with vigorous stirring for 45 min under N_2. After cooling to room temperature, the reaction was extracted twice with ether, and the organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using a 0–50% gradient of ethyl acetate in heptane to afford the desired product (4.25 g) as an oil. In this instance, the desired product was contaminated with 7.5 mol% of heptane, so a corrected mass of 4.1 g was used in calculating a yield of 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 16.0 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.12–7.22 (m, 2H), 2.67–2.75 (m, 2H), 2.60 (s, 3H), 1.62–1.73 (m, 2H), 1.32–1.44 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.98, 158.91, 152.60, 141.17, 136.93, 129.39, 124.02, 121.34, 40.89, 26.29, 24.51, 22.40, 13.85; HRMS (ESI): calcd for $C_{13}H_{18}NO$ $(M+H)^+$: 204.1383, found 204.1379.
26. *(±)-monomorine (1):* Compound **2** (0.300 g, 1.48 mmol) was dissolved in 40 mL of methanol/glacial acetic acid (3/1, v/v). The solution was degassed with nitrogen, and the catalyst (0.150 g, Johnson Mathey 5% Rh/C, #34, catalog number C101023-5) was added. The reaction mixture was placed in a Parr shaker under H_2 (45 psi) for 24 h at 50 °C. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuo. To the residue was added a saturated aqueous solution of $NaHCO_3$ (20 mL), resulting in pH of ca. 8-9. This solution was extracted twice with ethyl acetate, and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel (hexanes: ethyl acetate, gradient from 90:10–0:100) afforded the title compound as a light tan oil (0.150 g, 52%). Spectral and analytical data were consistent with literature values.[7]
27. Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603.