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Synthesis and Configuration of A *p*-Aminoacetophenonic Acid Isolated from Endophyte of the Mangrove Plant *Kandel candel*

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Keywords: amino acids / enones / natural products /aldols / condensation .

Two diastereomers of the title compound were synthesized through an enantioselective route, with the stereogenic center at the C-2 derived from a commercially available reagent and the one at the C-4 installed via Evans asymmetric aldol condensation. By comparison of ^{1}H and ^{13}C NMR as well as optical rotations the configuration of the natural product was as assigned as (2*R*,4*R*). Some interesting issues such as suppression of the undesired yet dominating formation of cyclic ethers associated with deprotection of a TBS protected terminal hydroxyl group and the previously unknown differences in ^{1}H NMR and IR between the end product separated by normal phase chromatography and that by reverse phase chromatography are also presented.

Introduction

In their search for active compounds as leads for drug discovery, Guo and Grabley investigated secondary metabolites of mangrove plants and their endophytes. The endeavour led to isolation of three *p*-aminoacetophenonic acids (**1**-**3**, Figure 1),[1] which had been suggested to be precursors of levorin[2] and trichomycin[3], the aminoacetophenone heptane antibiotics which have a wide spectrum of therapeutic activities. With the aid of modern spectroscopy the gross structures of these compounds were reliably assigned. However, the absence of e. g., OH groups at the stereogenic centers made it extremely difficult to elucidate the configurations.

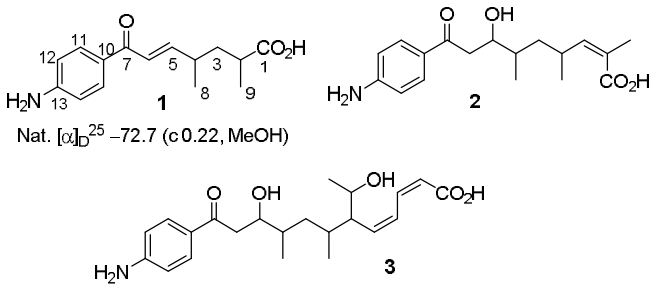
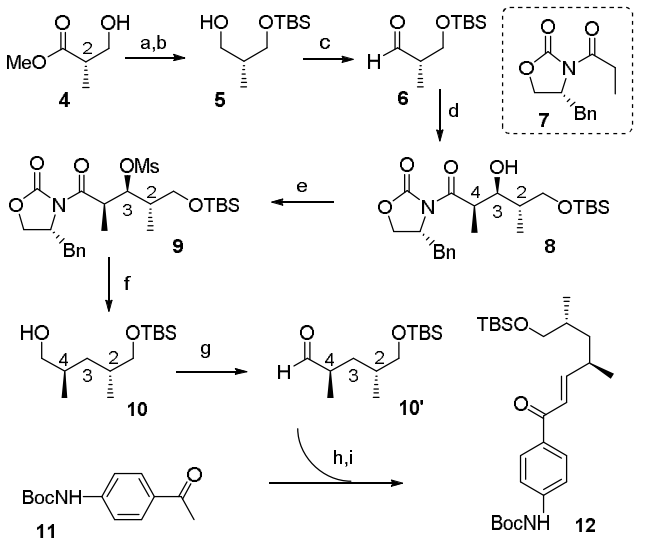


Figure 1. The structures for *p*-aminoacetophenonic acids **1**-**3**.

Here below we wish to report a synthetic endeavour, which allowed for establishment of the relative as well as absolute configuration of the *p*-aminoacetophenonic acid **1**.

Results and Discussion

The synthesis of (2*R*,4*R*)-**1** is shown in Scheme 1. The commercially available (*S*)-Roche ester **4** was protected[4] with TBSCl and reduced[5] with DIBAL-H to afford **5** according to the literature. Alcohol **5** was then subjected to Swern oxidation to give aldehyde **6**, which was directly used without any purification in the subsequent Evans[6a,b] aldol condensation with **7** to furnish the known[6b] aldol **8**.



Scheme 1. Reagents and conditions. a) TBSCl, imidazole, DMF, 100%; b) DIBAL-H, THF, 81%; c) Swern oxidation; d) nBu$_2$BOTf, **7**, Et$_3$N, CH$_2$Cl$_2$, 84% overall from **5**; e) MsCl. Et$_3$N, 75%; f) LiBH$_4$, THF-MeOH, 87%; g) Swern oxidation, 96%; h) LDA, THF, –78 °C, **11**, i) MsCl, Et$_3$N, 36% over 2 steps from **11**.

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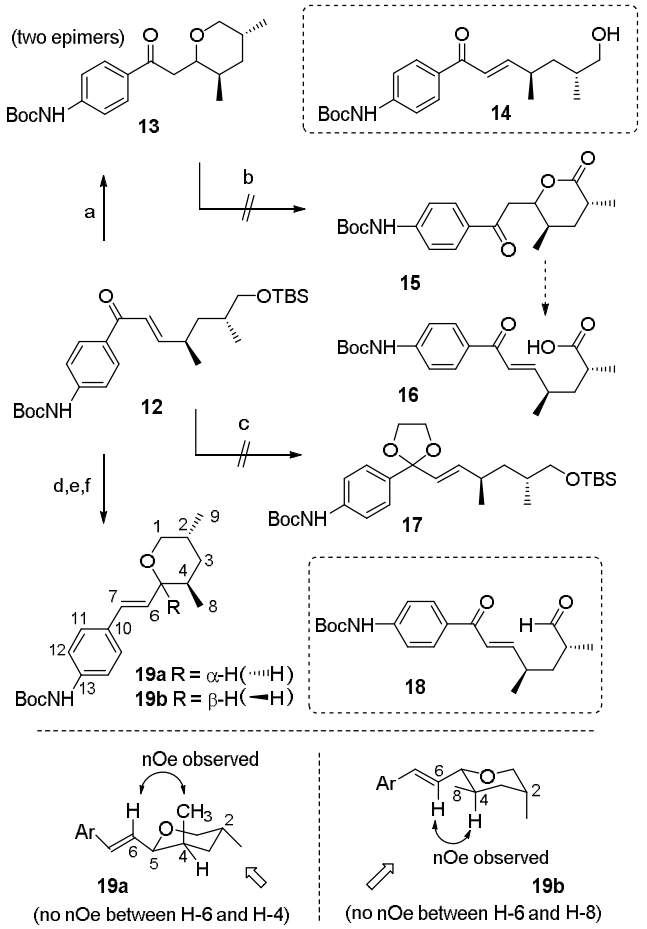
The OH group in **8** was mesylated with MsCl to give **9**, which was then treated with $LiBH_4$ to achieve concurrent deoxygenation at the C-3 and reductive removal of the chiral auxiliary to afford the known[7] alcohol **10**. Conversion of **10** into the corresponding aldehyde by Swern[8] oxidation ($DMSO/(COCl)_2/Et_3N$) followed by condensation with the carbanion of **11**[9] and elimination of the resulting OH after activation with MsCl furnished enone **12**.

Removal of the terminal TBS protecting group turned out to be far more complicated than one would possibly expect. Treatment **12** with nBu$_4$NF,[10a] or HF·py[10b] or $FeCl_3$/MeOH[10c] all led to undesired cyclic ether **13** (Scheme 2) as the predominant product (obtained as a mixture of two epimers), while the desired terminal alcohol **14** was obtained only in negligible quantities. Direct oxidation of **12** under Jones[11] conditions also led to **13**, while treating **12** with IBX[12] failed to result any reaction at all. $RuCl_3/NaIO_4$ oxidation[13] of **13** to afford lactone **15** (which was expected to undergo elimination/ring-opening on treatment with a proper base to provide **15**) also failed; no discernible reactions occurred.

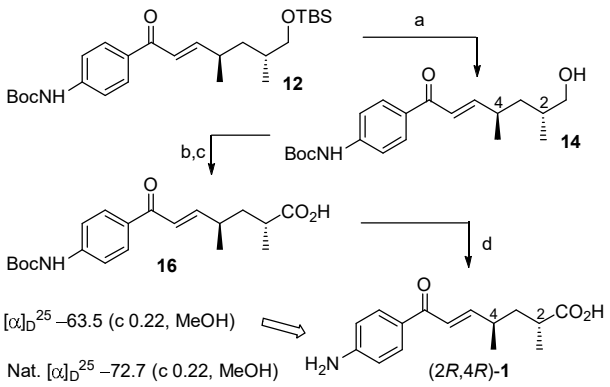


Scheme 2. Reagents and conditions. a) nBu$_4$NF, THF, or aq. HF, THF or HF·py, THF, or $FeCl_3$, MeOH, 70-90% of **13** along with negligible amounts of **14**; b) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; c) $HO(CH_2)_2OH$, $HC(OMe)_3$, p-TsOH; d) $NaBH_4$, $CeCl_3·7H_2O$, MeOH; e) nBu$_4$NF, THF, rt, 10 h, 66% over 2 steps from **12**; f) Dess-Martin periodinane, CH_2Cl_2, 35% of a mixture of **19a** and **19b** (3:2) over 3 steps from **12**.

To mask the enone moiety, which promoted the undesired intramolecular Michael addition to the enone subunit to afford **13**, we also tried to convert the enone carbonyl group into its ethylene glycol ketal under the $HO(CH_2)_2OH/HC(OMe)_3/p$-TsOH[14] conditions. Unfortunately, the reaction led to a mixture, presumably caused by intermolecular Michael addition of ethylene glycol and other side reactions. Reduction of the carbonyl group under the Luche[15] conditions ($NaBH_4/CeCl_3$/MeOH) gave the expected diol smoothly. However, subsequent Dess-Martin[16] oxidation of the intermediate diol did not result in aldehyde **18**. Instead, cyclic ether **19a** and **19b** (assigned with the aid of nOe's observed in the corresponding NOESY spectra) were obtained as the only isolable products.

As the attempts to avoid the predominating formation of **13** through masking the enone motif appeared unfeasible, we next turned to the possibility of suppressing the side reaction through reducing the catalysis for the ring-closing process: the 1,4-addition of the terminal OH to the enone is expected to be catalysed by either acid or base. TABF (nBu$_4$NF, often available as nBu$_4$NF·xH_2O) is known to be basic in the presence of H_2O (due to strong tendency to form HF). It thus appears that addition of equal molar amounts of a proper acid might neutralize the basicity of TBAF and consequently suppress the intramolecular Michael addition. Prompted by this thought, we then attempted to use 1:1 TBAF-AcOH[17] (glacial acetic acid) in deprotection of the TBS in silyl ether **12**.

To our delight, addition of equal molar amounts (with respect to TBAF) of AcOH indeed suppressed formation of **13** (8%) significantly, while the yield of desired **14** from previously negligible to 46%. However, the reaction became remarkably slow: Previously (i.e., in the absence of AcOH), it would take only 1 h for full consumption of the starting **12**. After introduction of AcOH, 45% of the starting **12** was recovered despite the prolonged reaction time (15 h). Increasing the substrate concentration from 0.1 M to 0.2 M under the otherwise the same conditions raised the yield of **14** to 55%, together with 8% of **13** and 37% of recovered **12**. Satisfactory results were eventually obtained by using 3 mol equiv (with respect to **12**) of 1:1 TBAF-AcOH (instead of 2 mol equiv as used in above experiments) and a substrate concentration of 0.2 M. Under such conditions, the starting **12** was practically fully consumed, giving 81% of **14** and only traces of **13** (Scheme 3).

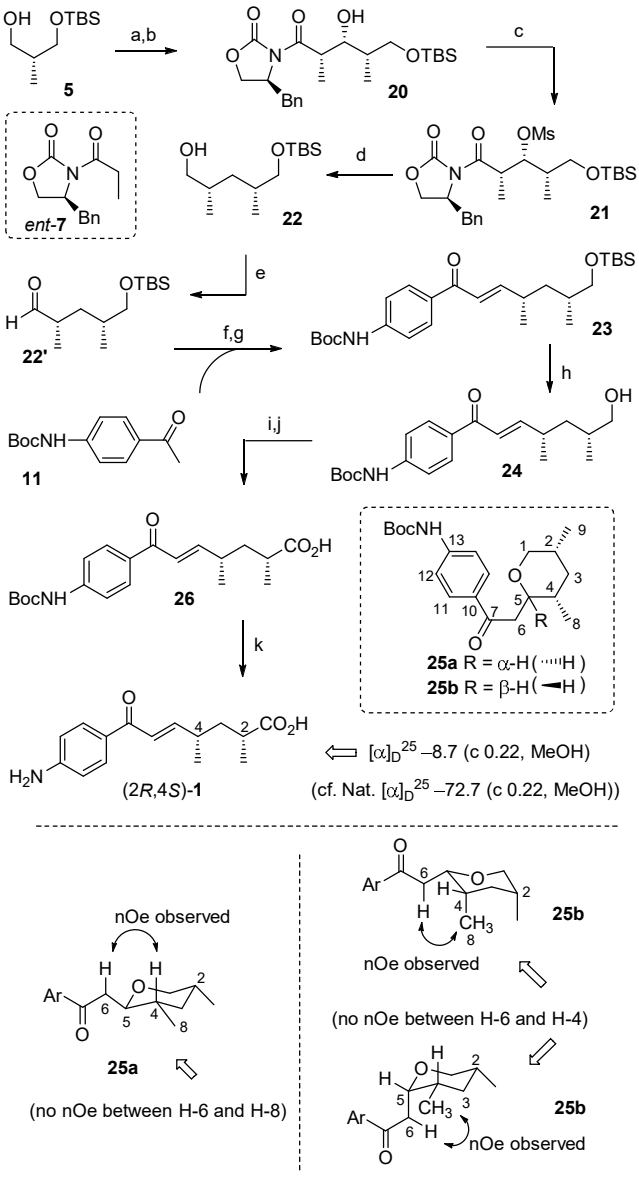


Scheme 3. Reagents and conditions. a) 1:1 nBu$_4$NF/AcOH, THF, rt, 81%; b) Dess-Martin periodinane, CH_2Cl_2; c) $NaClO_2$/2-methyl-but-2-ene/pH 7 phosphate buffer, 80% from **14**; d) CF_3CO_2H, 70%.

The isolated **14** was then oxidized with Dess-Martin periodinane to give the intermediate aldehyde, which was further treated with $NaClO_2$/2-methyl-but-2-ene/phosphate buffer (Pinnic[18] oxidation) to afford carboxylic acid **16**. The Boc protecting group in **16** was then removed with CF_3CO_2H to afford the end product (2*R*,4*R*)-**1**.

The ^{1}H and ^{13}C NMR of (2*R*,4*R*)-**1** were generally consistent with those reported in the literature (except that for the C-13, where the error was slightly larger than 0.5 ppm). And its optical rotation was measured to be $[\alpha]_D^{25}$ –63.5 (*c* = 0.22, MeOH), rather close to that for the natural product ($[\alpha]_D^{25}$ –72.7 (*c* = 0.22, MeOH)).

For comparison, we also synthesized (2*R*,4*S*)-**1** as shown in Scheme 4, starting with Swern oxidation of alcohol **5** as described above to afford the intermediate aldehyde. Subsequent Evans condensation was realized using *ent*-**7** instead of **7**. The resulting aldol was then mesylated and reduced with $LiBH_4$ to give alcohol **22**. Another Swern oxidation followed by condensation with **11** afforded enone **23** as planned.



Scheme 4. Reagents and conditions. a) Swern oxidation; b) nBu$_2$BOTf, *ent*-**7**, Et$_3$N, CH$_2$Cl$_2$, 88% over 2 steps from **6**; c) MsCl. Et$_3$N, 74%; d) $LiBH_4$, THF-MeOH, 76%; e) Swern oxidation, 92%; f) LDA, THF, –78 °C, **11**, g) MsCl, Et$_3$N, 52% over 2 steps from **11**; h) 1:1 nBu$_4$NF/AcOH, THF, 58% of **24** along with 44% of **25** (1:1 mixture of **25a** and **25b**); i) Dess-Martin oxidation, 97%; j) Pinnic oxidation, 82% from the intermediate aldehyde or 80% over 2 steps from **24**; k) CF_3CO_2H, 65%.

Then, somewhat unexpected, removal of the TBS protecting group in **23** turned out to be even more difficult than that of **12**. Under the conditions optimized for conversion of **12** into **14**, alcohol **24** was obtained in only 32% yield, along with as much as 50% of undesired ring-closure products **25a** and **25b** (assigned with the aid of their NOESY spectra).

Compared with generation of **13** from **14**, formation of **25** is apparently much more facile, presumably because of a more stable cyclic transition state (where both methyl groups could adopt an equatorial orientation). To suppress the chain folding, we decided to attempt the desilylation at low temperatures. We began with –20 °C, but failed to observe any reactions despite prolonged reaction time (15 h). At 0 °C, traces of **24** and **25** could be detected by TLC, but only after 30 h's reaction. As further extension of the reaction time was impractical, to run the desilylation at a higher substrate concentration seemed to be the only choice available remained. Gratifyingly, with the concentration of **23** raised from 0.2 M to 1.0 M, the deprotection at 0 °C went to completion within 23 h, affording the desired **26** in 58% yield (along with 45% of **25**). The isolated alcohol **26** was then subjected to Dess-Martin oxidation, Pinnick oxidation and removal of Boc group as described above for the (2*R*,4*R*)-**1** without any unexpected events and finally furnished the desired (2*R*,4*S*)-**1**.

The ^{1}H NMR of (2*R*,4*S*)-**1** was apparent different from what were reported for natural **1**: The H-4 and H-2 of (2*R*,4*S*)-**1** were well resolved, appearing as a distinct heptet at δ 2.48 and a clear-cut sextet at δ 2.42, respectively, rather than two unresolved multiplets as described in the literature. Similarly, the two protons at C-3 also were two well resolved double-triplets (not two unresolved multiplets as stated in the literature), respectively. Minor discrepancies were also found in ^{13}C NMR (cf. the Supporting Information). Finally, the optical rotation of (2*R*,4*S*)-**1** was found to be ($[\alpha]_D^{25}$ –8.7 (*c* = 0.22, MeOH)), which was definitely incompatible with that for natural **1** ($[\alpha]_D^{25}$ –72.7 (*c* = 0.22, MeOH)). Therefore, the (2*R*,4*S*) configuration could be excluded with high certainty, leaving (2*R*,4*R*) as the only possible configuration for natural **1**.

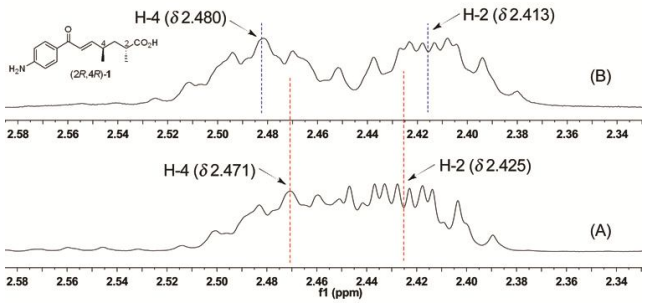


Figure 2. The δ 2.54-2.33 ppm region of the ^{1}H NMR for (2*R*,4*R*)-**1** obtained by normal phase chromatography (trace (A)) and that by reverse phase chromatography (trace (B)) recorded in CD_3OD under comparable conditions. Note that the H-4 and H-2 are closer to each other (at δ 2.471 and 2.425 ppm, respectively) in trace (A) compared with those (at δ 2.480 and δ 2.413 ppm, respectively) in trace (B).

Somewhat unusual of compound **1** and thus worth of mentioning is that the NMR, IR and optical rotation of the sample were slightly yet definitely different before and after an additional reverse phase chromatography. For example, the H-4 and H-2 in the ^{1}H NMR recorded on a sample of (2*R*,4*R*)-**1** separated by normal phase chromatography (eluting with 1:1 PE/EtOAc; PE = petroleum ether)

is shown in Figure 2 (bottom trace). This sample was then subjected to a reverse phase chromatography on C-18 (eluting with 1:1 H_2O/MeOH, as reported for natural **1**). The H-4 and H-2 in the ^1H NMR taken after the reverse phase chromatography (top trace, Figure 1) apparently moved away from each other, not so much but definitely unmistakable. And after this reverse phase chromatography, another normal phase chromatography of the same sample made the spacing between the H-4 and H-2 in ^1H NMR narrowed again, back to the original status (closer to each other, as in the bottom trace, Figure 1).[19] Discernible changes were also found in ^{13}C NMR and **optical** rotation after the reverse phase chromatography (cf. the Supporting Information).

To understand the rather confusing differences between the NMR of the sample obtained by normal phase chromatography and that by reverse phase chromatography, all potentially possible factors that might affect the spectra were considered, such as sample concentrations, contamination by traces of silica gel or C-18 silica gel and residual H_2O (which was used as co-eluent in the reverse phase chromatography). However, the NMR of a given (2*R*,4*R*)-**1** sample taken at different sample concentrations turned out just the same. Filtration of the sample solutions through commercially available polymer membrane filter to remove any silica gel or C-18 silica gel leaked from the chromatography column before rotary evaporation had no influence on the appearance of the ^1H NMR. Finally, addition of H_2O (sequentially 0.25 mg, 0.5, 1, and finally 3 mg, well-shaken after each addition) to the NMR sample solution (in CD_3OD) of (2*R*,4*R*)-**1** (obtained by normal phase chromatography) did not show any discernible effects; both the spacing between the H-4 and H-2 in the ^1H NMR and the profiles of the two signals remained unchanged in all experiments.

Since **1** is amino acid, the potential possibility of different extents of protonation of the NH_2 by the carboxylic OH as the cause for the above mentioned NMR differences once was also considered. In such case, the samples obtained under different chromatographic conditions are expected to undergo re-equilibrium in CD_3OD to give the same protonation status (because the influence of the chromatographic solvents no longer exists); the extent of protonation of the NH_2 by the carboxylic OH was decided only by the acidity of the solution. However, addition of traces of HCl (3 μL of a 0.05 M solution in CD_3OD) to the NMR solution of (2*R*,4*S*)-**1** did not lead to any discernible changes in ^1H NMR. Supporting arguments also came from the structure of **1**; the amino group in this case is an aromatic one, which is normally not as basic as aliphatic NH_2. Therefore, it does not seem very likely for the NH_2 to be protonated by the carboxylic acid, especially when a strongly electron-withdrawing ketone carbonyl group is present on the phenyl ring at a position para to the NH_2.

A critical clue to the cause of the above mentioned NMR differences between the sample obtained by normal phase chromatography and that by reverse phase chromatography was later found by IR: The spectrum of the former showed a huge background lump in the 3600-2200 cm^{-1} region (characteristic of hydrogen-bonded carboxylic OH, Figure 3, top). However, in the IR taken on the sample after a subsequent reverse phase chromatography, the lump essentially disappeared (Figure 2, bottom); unmistakably showing that the carboxylic OH was no longer hydrogen-bonded. In other words, the samples isolated under different chromatographic conditions were indeed different. Since the gross structure and the configuration of the sample cannot be changed (because the sample after the reverse phase chromatography could return to its original status by subjection to another normal phase chromatography), what can be different was the conformation/the hydrogen-bonding related solution structure.

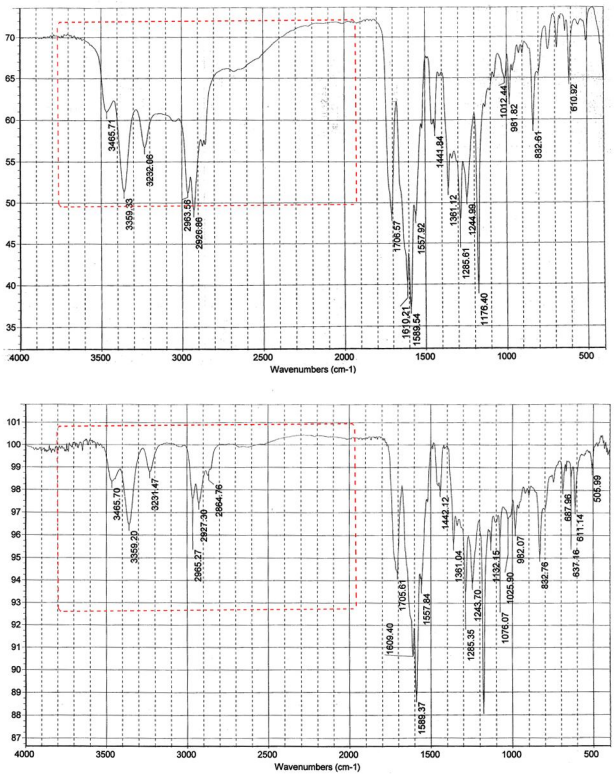


Figure 3. The IR of (2*R*,4*R*)-**1** before (top) and after (bottom) reverse phase chromatography, with the difference framed (the red dashed line boxes). For similar changes in IR of (2*R*,4*S*)-**1**, cf. the Supporting Information.

Under the given circumstances, the most plausible explanation appears to be that shown in Figure 4: When the sample was recovered after a normal phase chromatography (from a solution in 1:1 PE/EtOAc, both are non-protic solvents), there were no competing intermolecular hydrogen-bond donnors from the solvent molecules. Given the ketone carbonyl group (with an electron-donating NH_2 at the para position of the phenyl ring) being the most hydrogen-bond accetor in the molecule and the favorable location of the CO_2H, formation of the cyclic conformer through the intramolecular hydrogen bonding appeared to be the only possibility (Figure 4, the structure on the left).

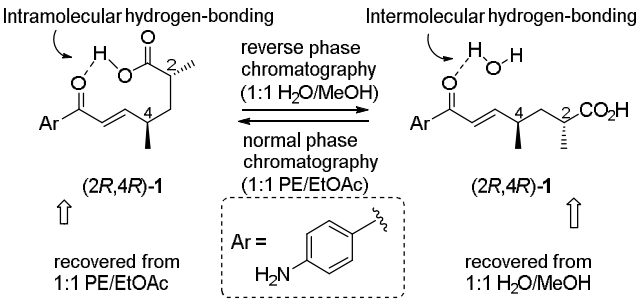


Figure 4. The (2*R*,4*R*)-**1** obtained by normal phase chromatography (left) and reverse phase chromatography (right) may have different types of hydrogen-bonding and consequently different conformations; cf. also the text. Note that the carboxylic group of the conformer on the right could also be hydrogen-bonded to H_2O or/and MeOH though not shown here.

In the case of reverse phase chromatography, compound **1** was dissolved in a large excess of H_2O and MeOH (hydrogen-bond donors). And probably while compound **1** was still on the C-18 silica gel, it was already in an open-chain conformation similar to that shown in Figure 4 (the structure on the right), with the ketone carbonyl (and very likely, also the carboxylic though for clarity not shown in Figure 4) group hydrogen-bonded to H_2O (which could be more than one in number, though for clarity not depicted) or/and MeOH. The situation remained unchanged until all solvents were removed by rotary evaporation and after dissolution in CD_3OD to form the NMR sample solution. When the sample by reverse phase chromatography was subjected to normal phase chromatography again, the hydrogen-bonded H_2O was absorbed by silica gel and thus led to formation of the intrmolecularly hydrogen-bonded "cyclic" conformer again.

Although in the NMR sample solution in CD_3OD a substantial portion of the "cyclic" conformer is expected to break up to give "non-cyclic" one(s) due to competing intermolecular hydrogen-bonding to the NMR solvent molecule, this process probably may never go to completion. This is because CO_2H was in the same molecule as the the ketone, it could never go far away from the ketone group and thus always had more chance to come back to form hydrogen-bond to the ketone group than any solvent molecules. As a consequence, at least a small portion of the intramolecularly hydrogen-bonded"cyclic" conformer may remain in the NMR sample solution and causes the aforementioned differences in e. g. ^{1}H NMR.

Conclusions

Two diastereomers of the title compound, a naturally occurring amino acid, were synthesized via an enantioselective route. Through comparison of the physical and spectroscopic data of the synthetic samples with those reported in the literature, the absolute configuration of the natural product was assigned to (2*R*,4*R*). En route to the total synthesis of the end products, a practical method for suppressing the undesired Michael addition of the terminal OH to form cyclic ether was developed. The relatively facile access to the synthetic samples also provided a good opportunity to look into this structurally unpretending compound. Some previously unnoticed properties/phenomena, such as the differences in the NMR, IR and optical rotation between the sample isolated by normal phase chromatography and that by reverse phase chromatography, were revealed for the first time. On the basis of the NMR and IR studies, the previously unknown (also rather confussing) spectroscopic differences between the samples obtained under different chromatographic conditions were attributed to the difference in the type of hydrogen-bonding to the ketone carbonyl group as a consequence of the chromatographic solvents employed. Although this interpretation may be not conclusive, the phenomena observed are definite and thus deserve special attention.

Experimental Section

General Methods.

Melting points were uncorrected (measured on a hot-stage melting point apparatus equipped with a microscope). Optical rotations were measured an Anton Paar MCP5500 polarimeter. IR spectra were measured with a Nicolet 380 infrared spectrophotometer. NMR spectra were recorded with a Bruker Avance III 400 NMR spectrometer (operating at 400 MHz for ^{1}H) or a Brucker Avance III HD 500 NMR (operating at 500 MHz for ^{1}H) or a Bruker Avance III HD 600 NMR (operating at 600 MHz for ^{1}H) instrument as stated below. ESI-MS data were acquired with a Shimadzu LCMS-2010 eV mass spectrometer or a Agilent Technologirs 6120 Quadrupole LC/MS. ESI-HRMS data were obtained with a Brucker Maxis 4 G TOF MS spectrometer or a Thermo Scientific Q Exactive HF Orbitrap-FT MS. Dry THF was obtained by distillation over Na/Ph_2CO under argon before use. Dry CH_2Cl_2 and Et_3N were obtained by distillation over CaH_2 under argon before use. All other solvents and reagents were used as received from commercial sources. Column chromatography was performed on silica gel (300-400 mesh) under slightly positive pressure. PE stands for petroleum ether (b. p. 60-90 °C).

Conversion of Roche ester to afford alcohol 5. To a solution of (*S*)-(+)-Roche ester (3.856 g, 32.7 mmol) in dry DMF (64 mL) stirred at ambient temperature were added imidazole (4.0 g, 58.8 mmol) and TBSCl (6.9 g, 45.8 mmol). Stirring was continued at the same temperature for 5 h (TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ (60 mL) was added to quench the reaction. The mixture was extracted with *n*-hexane (100 mL × 2). The combined organic layers were washed with water (30 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and careful rotary evaporation at 0 °C under aspirator vacuum left crude oil, which was purified by column chromatography (50:1 PE/EtOAc) on silica gel to give the known TBS protected Roche ester as a colorless oil (7.581 g, 32.7 mmol, 100%), which was directly used in the next step. The following data were acquired for this sample: $[\alpha]_D^{25}$ = +16.8 (*c* = 1.00, $CHCl_3$) (lit [20] $[\alpha]_D^{20}$ = +19.0 (*c* = 1.00, $CHCl_3$)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 9.7, 6.9 Hz, 1H), 3.68 (s, 3H), 3.65 (dd, *J* = 9.7, 6.1 Hz, 1H), 2.65 (dq, *J* = 6.0, 7.0 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 1.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.63, 65.38, 51.66, 42.66, 25.91, 18.35, 13.60, –5.36 ppm.

To a solution of the above obtained TBS protected Roche ester (7.581 g, 32.7 mmol) in dry THF (100 mL) stirred in an ice-water bath under argon (balloon) was added (via a syringe) slowly DIBAL-H (1.0 M, in hexanes, 75.21 mL, 75.21 mmol) over ca. 1 h. After completion of the addition, stirring was continued at ambient temperature for 3 h (TLC showed completion of the reaction). The reaction mixture was poured into a mixture of aq. sat potassium sodium tartrate (250 mL) and *n*-hexane (250 mL). The mixture was stirred vigorously for 1 h and then extracted with Et_2O (100 mL × 3). The combined organic layers were washed with water (30 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and careful rotary evaporation at 0 °C under aspirator vacuum left crude oil, which was purified by column chromatography (10:1 PE/EtOAc) on silica gel to give alcohol **5** as a colorless oil (5.410 g, 26.5 mmol, 81% overall from **4**). $[\alpha]_D^{25}$ = +7.7 (*c* = 2.38, CH_2Cl_2) (lit [4b] $[\alpha]_D^{20}$ = +9.79 (*c* = 2.38, CH_2Cl_2)). ^{1}H NMR (500 MHz,$CDCl_3$) δ 73.74 (ddd, *J* = 9.8, 4.4, 0.9 Hz, 1H), 3.67-3.58 (m, 2H) 3.55 (dd, *J* = 9.9, 8.0 Hz, 1H), 2.88 (dd, *J* = 7.0, 4.0 Hz, 1H), 1.99-1.90 (m, 1H), 0.90 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.90, 68.46, 37.18, 26.00, 18.32, 13.22, –5.40, –5.46. ppm.

Swern oxidation of 5 to afford aldehyde 6. A solution of DMSO (3.1 mL, 43.8 mmol) in dry CH_2Cl_2 (12 mL) was added very slowly to a solution of $(COCl)_2$ (2.3 mL, 26.3 mmol) in dry CH_2Cl_2 (100 mL) stirred at –78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 15 min. A solution of alcohol **5** (4.420 g, 21.9 mmol) in dry CH_2Cl_2 (30 mL) was introduced dropwise. Stirring was then continued at the same temperature for another 2 h. Finally, Et_3N (9.1 mL, 65.6 mmol) was added very slowly. The mixture was stirred at –78 °C for 5 min. The cooling bath was allowed to warm to 0 °C, at which the mixture was stirred for another hour. Water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and careful rotary evaporation at 0 °C under aspirator vacuum left crude aldehyde **6**[4b] as a yellowish oil (4.200 g, 21.00 mmol, 96%), which was used directly in the next step.

Evans aldol condensation of 6 to afford 8. nBu$_2$BOTf (1.0 M, in CH_2Cl_2, 17.8 mL, 17.8 mmol) was added to a solution of acyloxazolidinone **7** (3.760 g, 16.2 mmol) in dry CH_2Cl_2 (80 mL) stirred at –78 °C (EtOH-dry ice) under argon (balloon). Et_3N (3.1 mL, 22.6 mmol) was then introduced slowly. Stirring was continued at the same temperature for 10 min and then at 0 °C for 45 min. The bath temperature was then re-cooled to –78 °C. A solution of the above obtained crude aldehyde **6** (4.200 g, 21.0 mmol) in dry CH_2Cl_2 (30 mL) was introduced dropwise. Stirring was continued at –78 °C for 1 h and then at 0 °C for 2 h (TLC showed completion of the reaction). A solution of methanolic H_2O_2 (30 mL, with the stock solution prepared from 35 mL of aq. 30% H_2O_2 and 70 mL of MeOH). The mixture was stirred at 0 °C for 1 h before being washed with water (50 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (5:1 PE/EtOAc) on silica gel to afford aldol **8**[20] as a white solid (6.240 g, 14.3 mmol, 88% from **7**). M. p. 107-109 °C $[\alpha]_D^{25}$ = –21.3 (c = 1.00, $CHCl_3$) ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.36-7.26 (m, 3H), 7.26-7.20 (m, 2H), 4.72-4.67 (m, 1H), 4.24-4.15 (m, 2H), 4.08 (d, J = 2.2 Hz, 1H), 3.96-3.86 (m, 2H), 3.77 (dd, J = 9.9, 4.3 Hz, 1H), 3.65 (dd, J = 10.0, 7.4 Hz, 1H), 3.34 (dd, J = 13.3, 3.3 Hz, 1H), 2.77 (dd, J = 13.4, 9.7 Hz, 1H), 1.86-1.76 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H), 0.92-0.88 (m, 12H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.22, 153.33, 135.53, 129.57, 129.06, 127.43, 76.02, 68.41, 66.29, 55.85, 40.98, 37.88, 37.52, 26.00, 18.32, 13.18, 9.51, –5.43, –5.45 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3483, 2955, 2929, 2857, 1782, 1698, 1471, 1386, 1239, 1209, 1076, 1014, 984, 776, 750, 702 cm^{-1}; ESI-MS m/z 458.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{23}H_{37}NO_5SiNa$ ([M + Na]$^+$): 458.2333, found 458.2338.

Mesylation of 8 to afford 9. To a solution of aldol **8** (6.048 g, 13.9 mmol) in dry CH_2Cl_2 (80 mL) stirred in a 0 °C bath under argon (balloon) were added in turn Et_3N (10 mL, 69.5 mmol) and MsCl (4.3 mL, 55.6 mmol). After completion of the addition, the bath was removed. The mixture was stirred at ambient temperature for 2h (TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ (20 mL) was added, followed by water (20 mL). The mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (5:1 PE/EtOAc) on silica gel to afford **9** as a colorless oil (5.362 mg, 10.45 mmol, 75%). $[\alpha]_D^{25}$ = –81.8 (c = 1.00, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 3H), 7.26-7.19 (m, 2H), 5.08 (dd, J = 9.5, 2.2 Hz, 1H), 4.65-4.59 (m, 1H), 4.26-4.21 (m, 1H), 4.20-4.10 (m, 2H), 3.69-3.65 (m, 1H), 3.62 (dd, J = 10.0, 5.1 Hz, 1H), 3.28 (dd, J = 13.4, 3.4 Hz, 1H), 3.04 (s, 3H), 2.80 (dd, J = 13.4, 9.8 Hz, 1H), 2.01-1.92 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.0.4 (s, 3H) ppm; ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.76, 153.61, 135.49, 129.40, 128.88, 127.24, 82.42, 66.54, 64.04, 56.13, 39.87, 38.49, 37.86, 37.73, 25.79, 18.20, 13.58, 8.56, –5.45, –5.59 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 2948, 2927, 2857, 1781, 1702, 1456, 1384, 1361, 1250, 1213, 1177, 912, 837, 778, 703 cm^{-1}; ESI-MS m/z 536.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{24}H_{39}NO_7SSiNa$ ([M + Na]$^+$): 536.2109, found 536.2121.

$LiBH_4$ reduction of 9 to afford alcohol 10. To a solution of mesylate **9** (727 mg, 1.42 mmol) in dry THF (3 mL) stirred in an ice-water bath were added $LiBH_4$ (312 mg, 14.2 mmol) and MeOH (0.57 mL, 14.2 mmol). The mixture was stirred at ambient temperature for ca. 15 h (TLC showed completion of the reaction). With cooling (ice-water bath) and stirring, the excess hydride was quenched by careful addition of water (10 mL). The mixture was extracted with Et_2O (50 mL × 2). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (15:1 PE/EtOAc) on silica gel to furnish alcohol **10** as a colorless oil (304 mg, 1.24 mmol, 87%). $[\alpha]_D^{25}$ = +17.5 (c = 1.00, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51-3.42 (m, 2H), 3.42-3.37 (m, 2H), 1.79-1.68 (m, 2H), 1.52 (s, 1H), 1.21 (ddd, J = 13.7, 9.1, 4.7 Hz, 1H), 1.13 (ddd, J = 13.6, 9.1, 4.9 Hz, 1H), 0.91-0.88 (m, 12H),0.86 (d, J = 6.7 Hz, 3H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.18, 69.15, 36.99, 33.25, 33.10, 26.11, 18.52, 16.79, 16.61, –5.198, –5.203 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3364, 2956, 2928, 2857, 1472, 1385, 1256, 1097, 1037, 836, 775 cm^{-1}; ESI-MS m/z 269.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{13}H_{30}O_2SiNa$ ([M + Na]$^+$): 269.1919, found 269.1907.

Boc protection of 1-(4-aminophenyl)ethanone to afford 11. Di-t-butyl carbonate (Boc_2O, 24.2 g, 111.0 mmol) and K_2CO_3 (15.3 g, 111.0 mmol) were added in turn to a solution of commercially available 1-(4-aminophenyl)ethanone (5.003 g, 37.1 mmol) in dry DMF (100 mL) stirred at ambient temperature. The mixture was then stirred in a 100 °C oil bath for 3 h. The heating bath was then removed. The mixture was poured into ice-water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (15:1 PE/EtOAc) on silica gel to give **11** as a yellowish solid (5.516 g, 23.5 mmol, 63%). M. p. 145-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 2.56 (s, 3H), 1.53 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.07, 152.31, 143.09, 131.93, 129.96, 117.54, 81.40, 28.40, 26.49 ppm. FT-IR (film of a concd solution in CH_2Cl_2) ν = 3307, 2979, 1731, 1667, 1604, 1526, 1409, 1315, 1274, 1155, 1051, 959, 763 cm^{-1}; ESI-MS m/z 258.3 ([M + Na]$^+$); ESI-HRMS calcd for $C_{13}H_{17}O_3NNa$ ([M + Na]$^+$): 258.1101, found 258.1103.

Swern oxidation of 10 and subsequent condensation with 11 to afford 12. A solution of DMSO (1.3 mL, 18.2 mmol) in dry CH_2Cl_2 (5 mL) was added very slowly to a solution of $(COCl)_2$ (0.93 mL, 10.9 mmol) in dry CH_2Cl_2 (15 mL) stirred at –78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 15 min. A solution of alcohol **10** (1.794 g, 7.29 mmol) in dry CH_2Cl_2 (9 mL) was introduced dropwise. Stirring was then continued at the same temperature for another 2 h. Finally, Et_3N (1.5 mL, 36.5 mmol) was added very slowly. The mixture was stirred at –78 °C for 5 min. The cooling bath was allowed to warm to 0 °C, at which the mixture was stirred for another hour. Aq HCl (2%, 5 mL) was added. The mixture was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were washed with aq. sat. $NaHCO_3$ (5 mL), water (20 mL) and brine (5 mL), and then dried over anhydrous $MgSO_4$. Filtration and careful rotary evaporation at 10 °C under aspirator vacuum left the corresponding (low boiling) aldehyde **10'** as a yellowish oil (1.700 g, 6.97 mmol, 96% crude), which was used directly in the next step.

A solution of **11** (1.093 g, 4.65 mmol) in dry THF (14 mL) was added via a syringe to a solution of LiN(iPr)$_2$ (LDA, 2.0 M, in THF-n-heptane-ethylbenzene, 5.1 mL, 10.23 mmol) in dry THF (18 mL) stirred at –78 °C under argon (balloon), followed by a solution of the aldehyde **10'** obtained above (1.700 g, 6.97 mmol, crude and thus inaccurate) in dry THF (15 mL). The mixture was stirred at –78 °C for 4 h (TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ (30 mL) was added. The mixture, after warmed to ambient temperature, was extracted with Et_2O (100 mL × 2). The combined organic layers were washed with aq. HCl (1%, 30 mL), aq. sat. $NaHCO_3$ (30 mL) and brine (10 mL), and then dried over anhydrous $MgSO_4$. Filtration and rotary evaporation left the intermediate aldol, which was directly dissolved in in dry CH_2Cl_2 (18 mL) and stirred in an ice-water bath under argon (Balloon). To this solution (stirred) was added Et_3N (4.5 mL, 23.3 mmo), followed by MsCl (0.54 mL, 6.98 mmol). Stirring was continued at ambient temperature for 2 h (TLC showed completion of the reaction). Water (20 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were washed with aq. HCl (1%, 30 mL), aq. sat. $NaHCO_3$ (30 mL) and brine (10 mL), and then dried over anhydrous $MgSO_4$. Filtration and rotary evaporation left the intermediate aldol, which was purified by column

chromatography (15:1 PE/EtOAc) on silica gel to give enone **12** as a pale yellow solid (772 mg, 1.67 mmol, 36% from alcohol **11**). Data for enone **12**: M. p. 77-79 °C $[\alpha]_D^{25}$ = –9.6 (*c* = 0.47, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 6.96 (dd, *J* = 15.4, 7.8 Hz, 1H), 6.83 (dd, *J* = 15.4, 0.9 Hz, 1H), 6.69 (s, 1H), 3.45 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.41 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.52 (hept, *J* = 7.1 Hz, 1H), 1.69 (sext, *J* = 6.5 Hz, 1H), 1.53 (s, 9H), 1.51-1.44 (m, 1H), 1.27-1.18 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.91-0.88 (m, 12H), 0.04 (d, *J* = 2.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.65, 155.17, 152.31, 142.67, 132.77, 130.21, 123.63, 117.61, 81.41, 68.29, 39.98, 34.82, 33.52, 28.44, 26.10, 19.65, 18.50, 17.20, –5.20 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3315, 2957, 2928, 2856, 1753, 1661, 1618, 1593, 1411, 1367, 1314, 1231, 1157, 1094, 1054, 837, 775 cm^{-1}; ESI-MS *m/z* 484.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{26}H_{43}O_4NSiNa$ ([M + Na]$^+$): 484.2856, found 484.2854.

Luche reduction, desilylation and Dess-Martin oxidation of 12 to afford 19a and 19b. $NaBH_4$ (7.3 mg, 0.19 mmol) and $CeCl_3{\cdot}7H_2O$ (43 mg, 0.115 mmol) were added in turn to a solution of **12** (44 mg, 0.095 mmol) in MeOH (0.5 mL) stirred in an ice-water bath. Stirring was continued at the same temperature for 2 h (TLC showed completion of the reaction). Water (3 mL) was added. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (2 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue (42 mg, the intermediate alcohol), which was dissolved in THF (0.5 mL) and stirred in an ice-water bath. *n*Bu_4NF (1.0 M, in THF, 0.23 mL, 0.23 mmol) was added. Stirring was continued at ambient temperature for 10 h. Aq. sat. $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (2 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (1:1 PE/EtOAc) on silica gel to afford the intermediate diol as a colorless oil (21 mg, 0.0602 mmol, 66% over two steps from **12**). Part of this diol (15 mg, 0.043 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL) and stirred in an ice-water bath. Dess-Martin periodinane (73 mg, 0.172 mmol) was introduced. Stirring was then continued at ambient temperature for 30 min (TLC showed completion of the reaction). Water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine (2 mL) and dried over anhydrous Na_2SO_4. Filtration and rotary evaporation gave a residue, which was purified by column chromatography (10:1 PE/EtOAc) on silica gel to give **19a** (less polar than **19b**, 3 mg, 0.009 mmol, 21% from the desilylation product or 13.9% overall from **12**) and **19b** (more polar than **19a**, 2 mg, 0.006 mmol, 14% from the desilylation product or 9.2 % overall from **12**) as colorless oil.

Data for **19a** (a colorless oil): $[\alpha]_D^{25}$ = –35.4 (*c* = 0.20, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H, H-11, H-12), 6.50 (dd, *J* = 16.1, 1.5 Hz, 1H, H-7), 6.45 (s, 1H, NH), 6.08 (dd, *J* = 16.1, 5.4 Hz, 1H, H-6), 4.06-4.02 (m, 1H, H-5), 3.96 (ddd, *J* = 11.3, 4.7, 2.0 Hz, 1H, H-1), 3.07 (t, *J* = 11.1 Hz, 1H, H-1), 2.00-1.91 (m, 1H, H-2), 1.91-1.84 (m, 1H, H-4), 1.74-1.69 (m, 1H, H-3), 1.51 (s, 9H, *t*Bu Me), 1.45-1.38 (m, 1H, H-3), 1.00 (d, *J* = 7.0 Hz, 3H, H-8), 0.79 (d, *J* = 6.6 Hz, 1H, H-9) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, assigned with the aid of HSQC) δ 152.76 (quat, Boc carbonyl), 137.58 (quat, C-13), 132.31 (C-10), 129.16 (C-7), 128.52 (C-6), 127.09, 118.58, 80.77 (quat, *t*Bu), 80.44 (C-5), 75.40 (C-1), 39.88 (C-3), 33.24 (C-4), 28.48 (*t*Bu Me), 25.16 (C-2), 17.45 (C-9), 13.02 (C-8) ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3383, 2965, 2925, 2870, 1710, 1524, 1412, 1310, 1258, 1160, 1112, 1056, 967, 745, 618 cm^{-1}; ESI-MS *m/z* 354.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{29}O_3NNa$ ([M + Na]$^+$): 354.2040, found 354.2047.

Data for **19b** (a colorless oil): $[\alpha]_D^{-25}$ = +45.5 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H), 6.54 (dd, *J* = 16.0, 0.9 Hz, 1H, H-7), 6.46 (s, 1H, NH), 6.12 (dd, *J* = 16.0, 7.4 Hz, 1H, H-6), 3.74 (dt, *J* = 11.2, 2.0 Hz, 1H, H-1), 3.64 (dd, *J* = 11.2, 2.8 Hz, 1H, H-1), 3.48-3.45 (m, 1H, H-5), 1.86-1.79 (m, 1H, H-2), 1.79-1.72 (m, 1H, H-4), 1.66-1.61 (m, 1H, H-3), 1.51 (s, 9H, *t*Bu Me), 1.46-1.39 (m, 1H, H-3), 1.14 (d, *J* = 7.1 Hz, 3H, H-9), 0.82 (d, *J* = 6.6 Hz, 3H, H-8) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, assigned with the aid of HSQC) δ 152.73 (quat, Boc carbonyl), 137.80 (C-13), 132.02 (C-7), 131.93 (quat, C-10), 128.14 (C-6), 127.29, 118.50, 85.41 (C-5), 80.72 (quat, *t*Bu), 72.72 (C-1), 38.29 (C-3), 30.65 (C-4), 28.98 (C-2), 28.48 (*t*Bu Me), 18.36 (C-8), 17.39 (C-9) ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3444, 2962, 2924, 2854, 1730, 1527, 1412, 1367, 1258, 1156, 1112, 1054, 725, 618 cm^{-1}; ESI-MS *m/z* 354.3 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{29}O_3NNa$ ([M + Na]$^+$): 354.2040, found 354.2048.

Desilylation of 12 to afford alcohol 14. A solution of equal molar *n*Bu_4NF and AcOH (1 M, in THF, 0.47 mL, 0.47 mmol of each) was added to a solution of **12** (72 mg,0.16 mmol) in THF (0.3 mL) stirred in an ice-water bath. The mixture was then stirred at ambient temperature (ca. 23 °C) for 11 h (TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ (3 mL) was added. The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (2 mL) and then dried over anhydrous $MgSO_4$. Filtration and rotary evaporation left a crude oil, which was purified by column chromatography (2:1 PE/EtOAc) on silica gel to give first traces of the undesired cyclic ether **13** (a mixture of two epimers, less polar than **14**) and then the main product alcohol **14** as a colorless oil (45 mg, 0.13 mmol, 81%).

Data for the main product **14**: $[\alpha]_D^{25}$ = –6.9 (*c* = 0.70, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.96 (dd, *J* = 15.4, 7.8 Hz, 1H), 6.85 (d, *J* = 15.4, 1H), 6.77 (s, 1H), 3.54 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.47 (dd, *J* = 10.5, 6.3 Hz, 1H), 2.55 (hept, *J* = 7.1 Hz, 1H), 1.69 (sext, *J* = 6.6 Hz, 1H), 1.53 (s, 9H), 1.52-1.45 (m, 1H), 1.33-1.24 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.55, 154.73, 152.31, 142.76, 132.58, 130.21, 123.74, 117.59, 81.40, 68.18, 39.79, 34.72, 33.45, 28.42, 19.65, 17.01 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3439, 3309, 2964, 2927, 1731, 1660, 1594, 1529, 1367, 1234, 1156, 1054, 747 cm^{-1}; ESI-MS *m/z* 370.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{29}O_4NNa$ ([M + Na]$^+$): 370.1989, found 370.1990.

Data for side-product **13** (an inseparable mixture of two epimers): M. p. 95-97 °C. $[\alpha]_D^{25}$ = –8.9 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96-7.91 (m, 4H), 7.46-7.41 (m, 4H), 6.67 (s, 2H), 4.03-3.99 (m, 1H), 3.82 (ddd, *J* = 11.2, 4.7, 2.2 Hz, 1H), 3.62-3.57 (m, 2H), 3.55 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.21 (dd, *J* = 16.0, 7.7 Hz, 1H), 3.15 (dd, *J* = 15.6, 8.3 Hz, 1H), 3.06-2.98 (m, 2H), 2.80 (dd, *J* = 16.0, 5.2 Hz, 1H), 1.94-1.82 (m, 1H), 1.81-1.71 (m, 1H), 1.70-1.64 (m, 1H), 1.62-1.56 (m, 1H), 1.53 (s, 18H), 1.48-1.37 (m, 2H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.82, 197.38, 152.28, 152.26, 142.93, 142.79, 132.29, 132.10, 130.05, 129.95, 117.52, 117.46, 81.45, 81.42, 80.60, 76.38, 75.59, 72.83, 42.68, 41.97, 40.12, 38.48, 31.48, 30.60, 28.97, 28.42, 25.16, 18.39, 17.42, 17.38, 12.80 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3446, 2959, 2924, 2854, 1733, 1673, 1603, 1529, 1457, 1384, 1261, 1157, 1052, 1023 cm^{-1}; ESI-MS *m/z* 370.3 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{29}O_4NNa$ ([M + Na]$^+$): 370.1989, found 370.1992.

Conversion of **14** into carboxylic acid **16** via aldehyde **18**. Dess-Martin periodinane (110 mg, 0.26 mmol) was added to a solution of alcohol **14** (45 mg,0.13 mmol) in dry CH_2Cl_2 (1.7 mL) stirred in an ice-water bath. Stirring was then continued at ambient temperature for 20 min (TLC showed completion of the reaction. Et_2O (5 mL) was added, followed by aq. sat. $Na_2S_2O_3$ (2 mL). The mixture was extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine (2 mL) and then dried over anhydrous $MgSO_4$. Filtration and rotary evaporation left crude aldehyde **18** as a yellowish oil (44 mg, 0.13 mmol, 100%), which was used directly in the next step.

A portion of the above obtained aldehyde **18** (19 mg, 0.055 mmol) was dissolved in *t*BuOH (3-mL). To this solution (stirred in an ice-water bath) were added 2-methyl-buta-2-ene (23 µL, 0.275 mmol), a solution of NaH_2PO_4 (20 mg, 0.165 mmol) in water (0.4 mL), and a solution of $NaClO_2$

(15 mg, 0.165 mmol) in water (0.4 mL). The mixture was then stirred at ambient temperature for 10 min (TLC showed completion of the reaction). EtOAc (5 mL) was added, followed by water (1 mL). The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and rotary evaporation left crude oil, which was purified by column chromatography (2:1 PE/EtOAc) on silica gel to afford acid **16** as a colorless oil (16 mg, 0.044 mmol, 80% overall from **14**). $[\alpha]_D^{25}$ = –44.2 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 15.4 Hz, 1H), 6.86 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.57-2.48 (m, 2H), 1.89-1.83 (m, 1H), 1.53 (s, 9H), 1.52-1.46 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.30, 181.62, 152.76, 142.84, 132.49, 130.26, 125.08, 117.68, 81.52, 40.17, 37.48, 35.58, 28.42, 20.30, 17.87 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3327, 2925, 2855, 1735, 1708, 1660, 1595, 1528, 1457, 1412, 1368, 1155, 1054, 800 cm^{-1}; ESI-MS *m/z* 384.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{27}O_5NNa$ ([M + Na]$^+$): 384.1781, found 384.1776.

Removal of the Boc in 16 to afford (2*R*,4*R*)-1. CF_3CO_2H (0.1 mL, 1.35 mmol) was added to a solution of **16** (12 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) stirred in an ice-water bath. Stirring was then continued at ambient temperature for 1 h (TLC showed completion of the reaction). The mixture was diluted with EtOAc (5 mL), neutralized with aq. $NaHCO_3$ (1 M) to pH 5, and extracted with EtOAc (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and rotary evaporation left crude oil, which was purified by column chromatography (1:1 Pe/EtOAc) on silica gel to furnish (2*R*,4*R*)-**1** as a yellowish oil (6 mg, 0.023 mmol, 70%). The data for this sample (i.e., separated using normal phase chromatography): $[\alpha]_D^{25}$ = –63.5 (*c* = 0.22, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, *J* = 8.8 Hz, 2H), 6.97 (dd, *J* = 15.3, 0.9 Hz, 1H), 6.73 (dd, *J* = 15.3, 8.7 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 2.52-2.44 (m, 1H), 2.44-2.37 (m, 1H), 1.78 (ddd, *J* = 13.7, 9.7, 5.2 Hz, 1H), 1.43 (ddd, *J* = 14.0, 9.4, 5.0 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 190.60, 180.58, 155.70, 152.87, 132.66, 127.17, 126.28, 114.48, 41.74, 39.16, 36.95, 20.81, 18.60 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3466, 3359, 3232, 2964, 2927, 1707, 1610, 1590, 1558, 1442, 1361, 1286, 1245, 1176, 982, 833, 611 cm^{-1}; ESI-MS *m/z* 284.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{15}H_{19}NO_3Na$ ([M + Na]$^+$): 284.1257, found 284.1261.

The above sample obtained using normal phase chromatography was then subjected to reverse phase chromatography (eluting with 1:1 H_2O/MeOH) on C-18 silica gel and the following set of data for (2*R*,4*R*)-**1** (isolated using reverse phase chromatography) were collected: $[\alpha]_D^{25}$ = –55.9 (*c* = 0.22, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 15.3 Hz, 1H), 6.75 (dd, *J*=15.2, 8.7 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 2.54-2.45 (m, 1H), 2.45-2.36 (m, 1H), 1.79 (ddd, *J* = 13.7, 9.7, 5.2 Hz, 1H), 1.42 (ddd, *J* = 13.9, 9.3, 5.0 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 190.60, 181.29, 155.62, 153.01, 132.61, 127.15, 126.15, 114.43, 41.83, 39.57, 36.93, 20.78, 18.69 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3466, 3359, 3231, 2965, 2927, 2865, 1706, 1609, 1589, 1558, 1442, 1285, 1244, 1076, 1026, 982, 833 cm^{-1}; ESI-MS *m/z* 262.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{15}H_{20}O_3N$ ([M + H]$^+$): 262.1438, found 262.1438.

Evans aldol condensation of 6 to afford 20. This was performed using the same procedures described above for the "Evans aldol condensation of **6** to afford **8**" except that **7** was replaced by *ent*-**7**. Data for **20** (a white solid, 11.04 g, 25.4 mmol, chromatography using 5:1 PE/EtOAc, 88% from aldehyde **6**): M. p. 70-72 °C. $[\alpha]_D^{25}$ = +34.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.36-7.27 (m, 3H), 7.23-7.18 (m, 2H), 4.70-4.64 (m, 1H), 4.23-4.15 (m, 2H), 4.07 (dd, *J* = 6.7, 4.1 Hz, 1H), 3.97 (quint, *J* = 6.8 Hz, 1H), 3.75 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.63 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.31 (s, 1H), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.77 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.79-1.71 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 1.7 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.92, 152.86, 135.26, 129.56, 129.09, 127.53, 74.83, 67.98, 66.17, 55.29, 41.01, 37.91, 37.38, 26.00, 18.35, 13.63, 11.56, –5.45, –5.49 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3475, 2955, 2929, 2857, 1783, 1697, 1455, 1383, 1209, 1132, 1076, 1020, 972, 837, 777, 702 cm^{-1}; ESI-MS *m/z* 236.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{23}H_{38}O_5NSi$ ([M + H]$^+$): 436.2514, found 436.2513.

Mesylation of 20 to afford 21. This was performed using the same procedures described above for the "Mesylation of **8** to afford **9**" except that **8** was replaced by **20**. Data for **21** (a white solid, 9.567 g, 18.6 mmol, chromatography using 5:1:1 *n*-hexane/EtOAc/CH_2Cl_2, 74% from **20**): M. p. 135-137 °C. $[\alpha]_D^{25}$ = +63.2 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 3H), 7.22-7.18 (m, 2H), 5.02 (dd, *J* = 7.0, 3.7 Hz, 1H), 4.66-4.60 (m, 1H), 4.28-4.21 (m, 2H), 4.16 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.64 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.50 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.07 (s, 3H), 2.80 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.10-2.00 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 1.3 Hz, 6H). ppm; ^{13}C NMR (125 MHz,$CDCl_3$) δ 173.94, 153.55, 135.47, 129.57, 129.06, 127.47, 84.16, 66.58, 64.74, 56.00, 41.17, 38.73, 38.61, 37.93, 26.00, 18.35, 13.77, 11.15, –5.36, –5.38 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 2929, 1778, 1695, 13691, 1359, 1338, 1288, 1213, 1196, 1175, 1132, 1076, 905, 839, 812, 779, 704 cm^{-1}; ESI-MS *m/z* 514.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{24}H_{39}O_7NSSiNa$ ([M + Na]$^+$): 536.2109, found 536.2112.

$LiBH_4$ reduction of 21 to afford alcohol 22. This was performed using the same procedures described above for the "$LiBH_4$ reduction of **9** to afford alcohol **10**" except that **9** was replaced by **21**. Data for **22** (a colorless oil, 263 mg, 1.07 mmol, chromatography using 15:1 PE/EtOAc, 76% from **21**): $[\alpha]_D^{25}$ = –2.5 (*c* = 1.00, $CHCl_3$) (lit [22] $[\alpha]_D^{20}$ = –2.0 (*c* = 1.00, $CHCl_3$)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.46-3.39 (m, 2H), 3.37 (dd, *J* = 9.7, 6.3 Hz, 1H), 1.77-1.66 (m, 2H), 1.60 (s, 1H), 1.44 (dt, *J* = 13.6, 6.9 Hz, 1H), 0.94 (dd, *J* = 6.7, 0.7 Hz, 3H), 0.92-0.87 (m, 12H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.41, 68.37, 37.43, 33.44, 33.40, 26.10, 18.50, 17.97, 17.85, –5.23 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3444, 2956, 2928, 2857, 1471, 1257, 1196, 1095, 1076, 836, 775 cm^{-1}; ESI-MS *m/z* 247.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{13}H_{31}O_2Si$ ([M + H]$^+$): 247.2088, found 247.2090.

Swern oxidation of 22 and subsequent condensation with 11 to afford 23. This was performed using the same procedures described above for the "Swern oxidation of **10** and subsequent condensation with **11** to afford **12**" except that **10** was replaced by **22**. Data for **23** (a yellowish solid, 788 mg, 1.71 mmol, chromatography using 15:1 PE/EtOAc, 52% from **11**): M. p. 64-66 °C. $[\alpha]_D^{25}$ = +5.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 15.4, 7.7 Hz, 1H), 6.76 (s, 1H), 3.41 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.37 (dd, *J* = 9.8, 6.2 Hz, 1H), 2.58-2.49 (m, 1H), 1.68-1.59 (m, 1H), 1.58-1.53 (m, 1H), 1.52 (s, 9H), 1.18-1.12 (m, 1H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.90-0.85 (m, 12H), 0.02 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.56, 154.56, 152.31, 142.68, 132.66, 130.19, 124.03, 117.57, 81.36, 68.54, 40.16, 34.91, 33.60, 28.41, 26.08, 20.80, 18.48, 16.83, –5.22, –5.24 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3314, 2957, 2929, 2857, 1735, 1662, 1593, 1528, 1411, 1314, 1231, 1157, 1093, 1054, 837 cm^{-1}; ESI-MS *m/z* 462.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{26}H_{44}O_4NSi$ ([M + H]$^+$): 462.3034, found 462.3036.

Desilylation of 23 to afford alcohol 24. A solution of equal molar *n*Bu_4NF and AcOH (1 M, in THF, 1.96 mL, 1.0 mmol of each) was added to a flask containing **23** (82 mg,0.178 mmol) stirred at 0 °C bath (controlled by a cooling pump system). The mixture was then stirred at 0 °C for 23 h (TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ (5 mL) was added. The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (2 mL) and then dried over anhydrous $MgSO_4$. Filtration and rotary evaporation left a crude oil, which was purified by column chromatography (2:1 PE/EtOAc) on silica gel to give first the undesired cyclic ether **25** (less polar than **24**) as a pair of epimers

(ca. 1:1, could be separated, 27 mg in total, 0.078 mmol, total yield 44%) and then the main product alcohol **24** as a colorless oil (36 mg, 0.104 mmol, 58%).

Data for **24**: $[\alpha]_D^{25}$ = +22.9 (*c* = 1.00, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.91-6.83 (m, 2H), 6.90 (s, 1H), 3.47 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.43 (dd, *J* = 10.5, 6.3 Hz, 1H), 2.60-2.51 (m, 1H), 1.69-1.60 (m, 1H), 1.60-1.54 (m, 1H), 1.53 (s, 9H), 1.24-1.17 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.56, 154.18, 152.38, 142.86, 132.45, 130.20, 124.23, 117.61, 81.34, 68.49, 40.02, 34.89, 33.72, 28.40, 20.90, 16.53 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3439, 3307, 2963, 2927, 1731, 1660, 1594, 1530, 1411, 1367, 1314, 1235, 1151054, 985, 838, 777 cm^{-1}; ESI-MS *m/z* 348.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{20}H_{30}O_4N$ ([M + H]$^+$): 348.2169, found 348.2171.

Data for side product **25a** (recored on a pure analytical sample obtained by further chromatoragphy, less polar than **25b**): $[\alpha]_D^{25}$ = +8.5 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.75 (s, 1H, NH), 3.77 (ddd, *J* = 11.2, 4.4, 2.3 Hz, 1H, H-1), 3.54 (ddd, *J* = 9.8, 8.4, 3.2 Hz, 1H, H-5), 3.11 (dd, *J* = 15.5, 8.4 Hz, 1H, H-6), 3.01 (dd, *J* = 15.5, 3.3 Hz, 1H, H-6), 2.93 (t, *J* = 11.1 Hz, 1H, H-1), 1.84-1.77 (m, 1H, H-3), 1.77-1.68 (m, 1H, H-2), 1.59-1.53 (m, 1H, H-4), 1.53 (s, 9H, *t*Bu), 0.92-0.83 (m, 1H, H-3), 0.88 (d, *J* = 6.6 Hz, 3H, H-8), 0.76 (d, *J* = 6.6 Hz, 3H, H-9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, assigned with the aid of HSQC) δ 197.95 (quat, C-7), 152.30 (quat, Boc carbonyl), 142.85, 132.26, 130.04 (quat, C-10), 117.46 (quat, C-13), 81.36 (quat, *t*Bu), 80.12 (C-5), 74.64 (C-1), 42.54 (C-6), 41.77 (C-3), 35.95 (C-4), 31.48 (C-2), 28.41 (*t*Bu Me), 18.19 (C-8), 17.23 (C-9) ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3333, 2955, 1732, 1672, 1603, 1528, 1410, 1318, 1231, 1157, 1096, 1053, 851 cm^{-1}; ESI-MS *m/z* 348.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{20}H_{30}O_4N$ ([M + H]$^+$): 348.2169, found 348.2169.

Data for side product **25b** (recorded on a pure analytical sample obtained by further chromatoragphy, more polar than **25a**): $[\alpha]_D^{25}$ = –54.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 6.82 (s, 1H, NH), 4.46 (dt, *J* = 9.4, 4.8 Hz, 1H, H-5), 3.54 (ddd, *J* = 11.6, 4.6, 1.7 Hz, 1H, H-1), 3.29-3.21 (m, 2H, H-6 and H-1), 2.94 (dd, *J* = 15.1, 4.7 Hz, 1H, H-6), 2.12-2.04 (m, 1H, H-4), 1.79-1.71 (m, 1H, H-2), 1.71-1.62 (m, 1H, H-3), 1.53 (s, 9H, *t*Bu), 1.07 (dt, *J* = 13.3, 11.3 Hz, 1H, H-3), 0.88 (d, *J* = 7.0 Hz, 3H, H-8), 0.85 (d, *J* = 6.7 Hz, 3H, H-9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.73 (quat, C-7), 152.30 (quat, Boc carbonyl), 142.97, 131.80, 129.86 (quat, C-10), 117.59 (quat, C-13), 81.37 (quat, *t*Bu), 74.00 (C-5), 67.45 (C-1), 35.83 (C-3), 35.18 (C-6), 33.62 (C-4), 31.13 (C-2), 28.40 (Boc Me), 17.85 (C-8), 17.78 (C-9) ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3333, 2955, 1732, 1672, 1590, 1528, 1409, 1367, 1290, 1233, 1156, 1077, 1052 cm^{-1}; ESI-MS *m/z* 348.3 ([M + H]$^+$); ESI-HRMS calcd for $C_{20}H_{30}O_4N$ ([M + H]$^+$): 348.2169, found 348.2171.

Conversion of 24 into carboxylic acid 26. This was performed using the same procedures described above for the "Conversion of **14** into carboxylic acid **16** via aldehyde **18**" except that **14** was replaced by **24**. Data for **26** (a colorless oil, 30 mg, 0.083 mmol, chromatography using 2:1 PE/EtOAc, 82% from the intermediate aldehyde **24'** or 80% over two steps from alcohol **24**): $[\alpha]_D^{25}$ = +4.4 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.92-6.85 (m, 2H), 2.57-2.45 (m, 2H), 1.94-1.87 (m, 1H), 1.53 (s, 9H), 1.51-1.43 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.33, 181.98, 152.98, 142.85, 132.42, 130.24, 124.44, 117.69, 81.52, 39.70, 37.43, 35.28, 28.42, 20.04, 17.30 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3438, 3334, 2964, 2919, 1730, 1701, 1655, 1561, 1384, 1150, 1052, 902, 836, 770 cm^{-1}; ESI-MS *m/z* 384.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{20}H_{27}O_5NNa$ ([M + Na]$^+$): 384.1781, found 384.1779.

Removal of the Boc in 26 to afford (2*R*,4*S*)-1. This was performed using the same procedures described above for the "Removal of the Boc in **16** to afford (2*R*,4*R*)-**1**" except that **16** was replaced by **26**.

Data for (2*R*,4*S*)-**1** (a colorless oil, 14 mg, 0.054 mmol, normal phase chromatography using 1:1 PE/EtOAc, 65% from **26**): $[\alpha]_D^{25}$ = –8.7 (*c* = 0.22, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, *J* = 8.8 Hz, 2H, H), 6.97 (dd, *J* = 15.3, 0.9 Hz, 1H), 6.74 (dd, *J* = 15.3, 8.4, Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 2.48 (hept, *J* = 7.1 Hz, 1H), 2.42 (sext, *J* =7.1 Hz, 1H), 1.81 (dt, *J* = 13.7, 7.8 Hz, 1H), 1.42 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 190.60, 180.55, 155.66, 153.03, 132.66, 127.18, 125.68, 114.50, 41.36, 38.89, 36.56, 20.49, 17.94 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3467, 3358, 3231, 2968, 2931, 1706, 1589, 1558, 1361, 1286, 1176, 1132, 982, 833 cm^{-1}; ESI-MS *m/z* 284.4 ([M + Na]$^+$); ESI-HRMS calcd for $C_{15}H_{19}O_3NNa$ ([M + Na]$^+$): 284.1257, found 284.1263.

The above sample obtained using normal phase chromatography was then subjected to reverse phase chromatography (eluting with 1:1 H_2O/MeOH) on C-18 silica gel and the following set of data for (2*R*,4*S*)-**1** (isolated using reverse phase chromatography) were collected: $[\alpha]_D^{25}$ = –8.6 (*c* = 0.22, MeOH). ^{1}H NMR (500 MHz, CD_3OD) 7.78 (d, *J*=8.8 Hz, 2H), 6.97 (d, *J* = 15.3 Hz, 1H), 6.77 (dd, *J* = 15.3, 8.3, Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 2.50 (hept, *J* = 7.1 Hz, 1H), 2.42 (sext, *J* = 7.1 Hz, 1H), 1.82 (dt, *J* = 13.5, 7.7 Hz, 1H), 1.40 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 190.60, 181.86, 155.54, 153.30, 132.55, 127.10, 125.41, 114.39, 41.56, 39.63, 36.46, 20.30, 18.16 ppm; FT-IR (film of a concd solution in CH_2Cl_2) ν = 3473, 3357, 3231, 2967, 2928, 2870, 1706, 1610, 1589, 1361, 1286, 1176, 1132, 1018, 832 cm^{-1}; ESI-MS *m/z* 262.2 ([M + H]$^+$); ESI-HRMS calcd for $C_{20}H_{30}O_4N$ ([M + H]$^+$): 262.1438, found 262.1439.

Supporting Information Copies of the ^{1}H and ^{13}C NMR spectra, FT-IR spectra for all new compounds, comparison tables of NMR and optical rotation data, comparison of ^{1}H NMR (expansions) and IR spectra recored on samples obtained under different chromatographic conditions.

Acknowledgments

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[19] The ^{1}H NMR of (2*R*,4*S*)-**1** obtained by normal phase chromatography remained unchanged after heating with a hiar dryer for several minutes (CD_3OD began to reflux in the NMR tube). And the spectrum of (2*R*,4*S*)-**1** siolated by reverse phase chromatography remained the same at rt over 43 h. Similar spectroscopic differences were also observed with (2*R*,4*S*)-**1** (cf. the Supporting Information).

[20] A. Millan, P. D. G. Martinez, V. K. Aggarwal, *Chem. Eur. J.* **2018**, *24*, 730-735.

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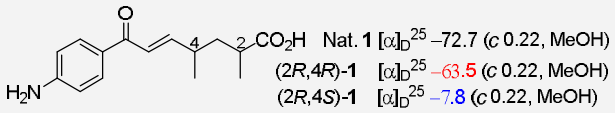
Layout 2:

Natural Product Synthesis



Although as a target of total synthesis and structural assignment of natural products a molecule of this size and complexity might never catch much attention, there is still something unusual and very interesting here --- the NMR, IR and optical rotation were actually dependent on, to everyons' surprise, the chromatographic conditions employed…

Xin Xiong, Yikang Wu* and Bo Liu*
……..... Page No. – Page No.

Synthesis and Configuration of A *p*-Aminoacetophenonic Acid Isolated from Endophyte of the Mangrove Plant *Kandel candel*

Keywords: amino acids / enones / natural products /aldols / condensation

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Supporting Information

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