Enantioselective Synthesis of 4-Acetylaminocyclopent-2-en-1-ols from Tricyclo[5.2.1.0^{2,6}]decenyl Enaminones. Precursors for 5′-Norcarbocyclic Nucleosides and Related Antiviral Compounds

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An efficient synthesis of both (1*S*,4*R*) and (1*R*,4*S*)-4-*N*-acetylamino-1-benzoylcyclopent-2-enes **33** has been accomplished starting from enantiopure 5-(1′-phenylethylamino)-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-ones **14** and **15**. N-Acetylation of both **15** and **14** followed by single electron-transfer reduction using lithium in liquid ammonia afforded diastereomeric mixtures of β-amino ketones **26** and **27** and of *ent*-**26** and *ent*-**27** in high yields and with high diastereoselectivity. In this reduction process, the enaminone double bond is reduced with the concomitant removal of the α-methylbenzyl group as the chiral auxiliary. Thermolysis of the respective diastereomic mixtures of **26** and **27** in the gas phase (FVT) or in solution afforded 4-*N*-acetylaminocyclopent-2-ene-1-ones **30** in high optical and chemical yields. Acidic hydrolysis of (+)-**30** gave (*R*)-(+)-4-aminocyclopentenone **31** as its hydrochloride. Stereoselective reduction of **30** using sodium borohydride and cerium chloride heptahydrate furnished amido alcohol **32**, which was isolated and characterized as its benzoyl derivative **33**.

Introduction

With the discovery that carbocyclic nucleosides exhibit pronounced antiviral activities,[1] recent years have witnessed an upsurge in research related to the synthesis of these compounds and their analogues. Naturally occurring carbocyclic nucleosides such as aristeromycin (**1**), obtained from *Streptomycis citricolor*,[2] and neplanocin A (**2**), isolated from *Actinoplanacea ampullariella*,[3] all display significant biological activity (Figure 1). However, the antiviral potential of aristeromycin[4] has been limited by its cytotoxicity, which arises from the biological consequences of its 5′-triphosphate metabolite.[5] Neplanocin A (**2**) has been found to exhibit antileukemic activity, and it is less toxic.[3] Carbovir (**3**)[6] and 1592U89 (**4**)[7] are synthetic carbocyclic nucleosides that also have interesting antiviral activities. Recently, Schneller and co-workers reported that 5′-norаristeromycin (**5**),[8] which is a desmethylene analogue of **1**, shows similar antiviral activity but without significant cytotoxicity. Since then, the synthesis of 5′-norаristeromycin[9] and various analogues of 5′-norcarbocyclic nucleosides have been reported and their biological activities evaluated.[10]

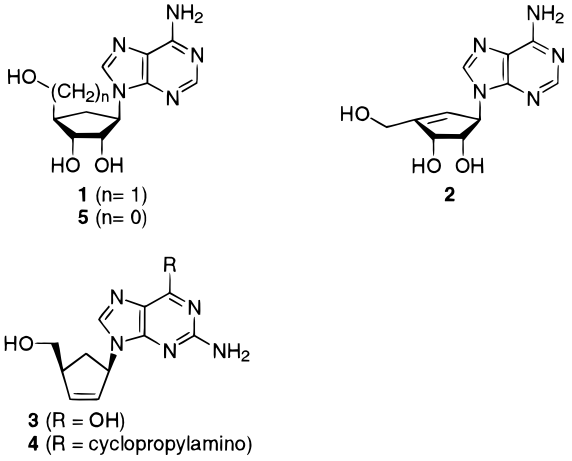

Figure 1.

Basic building blocks for the synthesis of these 5′-norcarbocyclic nucleosides constitute suitably substituted aminocyclopentenols **6** (Figure 2).[11] General approaches

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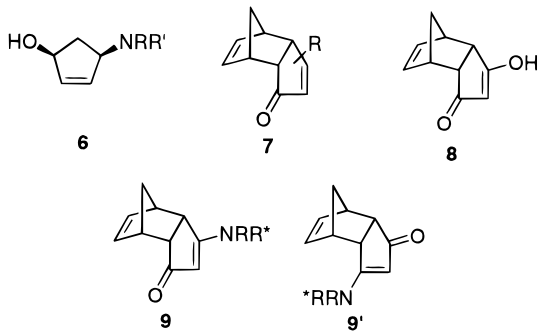
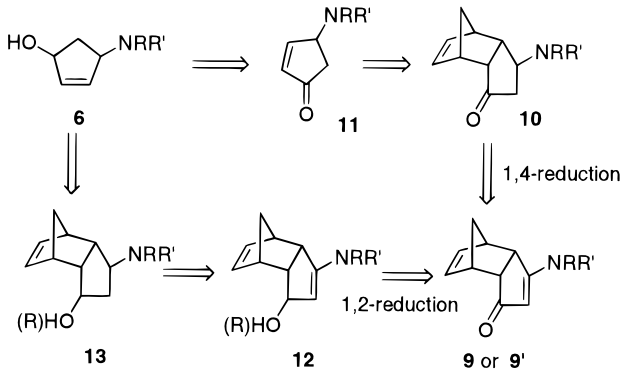


Figure 2.

to **6** involve (a) the cycloaddition of appropriate nitroso compounds with cyclopentadiene followed by hydrolysis,[8b,10a,b,11b,c,e,f] (b) the displacement of hydroxy group or its derivatives in mono- or diprotected 1,4-dihydroxycyclopent-2-ene by an amino[8a,10d,j] or azido[11g] function, (c) opening of epoxy cyclopentene by purine bases,[9] and (d) rearrangement of 4-amino substituted cyclopentene oxide.[11a] In recent years, we[12] and others[13,14] have demonstrated that the *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one system **7** is a highly useful synthon for a wide range of naturally occurring cyclopentanoids and other pharmacologically important structures. Recently, we reported on the asymmetric desymmetrization of pseudo-*meso*-5-hydroxy-*endo*-tricyclodecadienone **8** by chiral amines affording the readily separable diastereomeric tricyclic enaminones **9** and **9′** in excellent yields.[15] These tricyclic enaminones are attractive chirons as they could provide a convenient entry to the enantioselective synthesis of aminocyclopentenols **6** applying the cycloreversion methodogy as depicted in Scheme 1. Selective 1,4-reduction of **9** would give β-aminoketone **10**, which on [4 + 2]-cycloreversion gives access to the valuable γ-aminocyclopentenones **11**. These γ-aminocyclopentenones, although reported in some specific cases as precursors in the synthesis of prostanoids,[16] carbanucleosides, antiviral dipeptide isosteres,[17] and thienamycin,[18] have so far not been extensively studied, clearly due to the lack

Scheme 1



of a general and efficient access to these compounds. The present routes to this class of compounds involve the oxidation of amino alcohols[17−19] and the nucleophilic 1,4-addition of amines to suitably functionalized 4-hydroxycyclopentenones.[20,21] Subsequent carbonyl reduction in **11** would afford the desired aminocyclopentenols **6**. Alternatively, 1,2-reduction of the enaminone system in **9** may lead to tricyclic enamines **12**, which, then, in a second regioselective reduction step can be converted into tricyclic amino alcohols **13**, which on cycloreversion are expected to give aminocyclopentenols **6**. In this paper, we disclose a general and enantioselective synthesis of γ-aminocyclopentenones **11** including the parent amino compound (**11**, R, R′= H), which so far had not been prepared, and their stereo- and regioselective reduction to *cis*-amino alcohols **6**, starting from appropriately substituted homochiral tricyclic enaminones **9** and **9′**, essentially following the strategy as depicted in Scheme 1.[22]

Results and Discussion

N-α-Methylbenzyl-substituted tricyclic enaminones **14** and **15** were selected as the most appropriate substrates to test the synthetic strategy shown in Scheme 1 because (i) both diastereomers are readily available from γ-hydroxytricyclodecadienone (**8**) in optically pure form[15] and (ii) the chiral auxiliary, namely the α-methylbenzyl group, can in principle be reductively removed, considerably enhancing the synthetic potential of this methodology. The first step in our synthetic approach requires a chemo- and regioselective reduction of either the C_4-C_5 enaminone double bond or the C_3-ketone function in **14** and **15**. A wide range of hydride reagents was employed to effect this conversion,[23] but none of them proved successful. The conventional reagents either refused to reduce the enaminone moiety in **14** and **15** at all or, if reduction had occurred, a mixture of inseparable compounds was obtained. In some cases, parent *endo*-tricyclo-[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (**17**) was isolated from **14**, indicating the intermediacy of β-amino ketone **16** (Figure 3), which under the reaction conditions is apparently not

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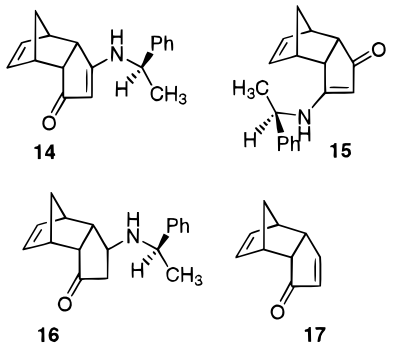
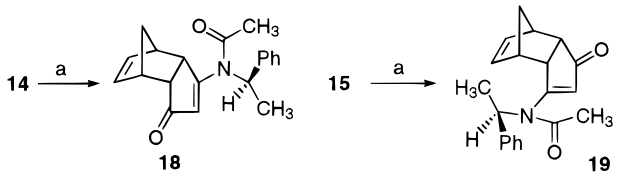


Figure 3.

Scheme 2[a]



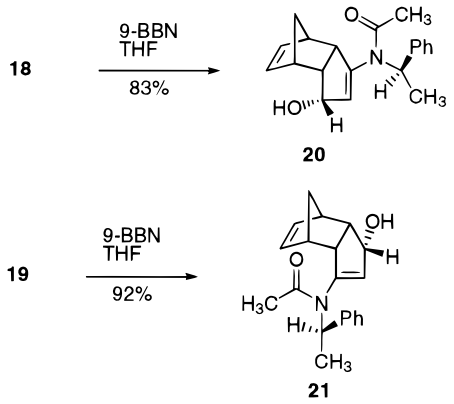
[a] Key: (a) NaH, CH_3COCl, THF, 89%.

stable but immediately undergoes elimination of the β-amino functionality.

The reluctance of the enaminone moiety in **14** and **15** to undergo hydride reduction under relatively mild conditions may be attributed to its pronounced π-delocalization, which decreases its electrophilicity in such a manner that rather harsh reduction conditions are necessary leading to nonselective reactions. We hypothesized that the introduction of an electron-withdrawing group on nitrogen might possibly circumvent this problem. For this purpose, *N*-acetyl derivatives **18** and **19** were prepared by acetylation of **14** and **15**, respectively, using sodium hydride and acetyl chloride in THF (Scheme 2).

Hydride Reduction of *N*-Acetyl Enaminones 18 and 19. Selective reduction of **18** and **19** was attempted again with a variety of reducing agents. In some cases the lability of the *N*-acetyl group interfered with the reduction method. Thus, the use of sodium borohydride in MeOH led to complete removal of the amide bond in **18** or **19** to give the original enaminones **14** or **15**, respectively. The use of more reactive metal hydrides appeared rather unselective and led, among other reaction pathways, to reduction of the acetamide function, producing mixtures of compounds. The use of metal hydrides therefore seemed unsuited for selective 1,2- or 1,4-reduction of enaminones **18** and **19**. Brown and coworkers[24] reported that 9-BBN was an ideal reagent for the selective reduction of ketone carbonyls in the presence of a wide variety of other functional groups. When this reagent was applied to enaminones **18** and **19**, a highly selective 1,2-reduction took place to give the respective *endo*-alcohols **20** and **21** as single compounds, in 83% and 92% yield, respectively (Scheme 3).

Scheme 3



The next step in our route to aminocyclopentenols **6** is the regioselective reduction of the remaining C_4-C_5 enamine double bond (Scheme 1). The susceptibility of the norbornene C_8-C_9 double bond toward catalytic hydrogenation necessitates the temporary protection of this double bond in order to allow selective hydrogenation of the enamine double bond. An elegant protection involves the use of the *endo* configuration of the C_3-hydroxyl function. Ogasawara et al.[25] have shown for related tricyclic *endo*-alcohols that halogenation of **20** or **21** using *N*-halosuccinimides may lead to the cyclic ethers **22** and **23**, respectively, by intramolecular attack of the *endo*-alcohol function at the intermediate halonium ion. Regeneration of the original double bond is eventually accomplished by reductive halogen elimination using activated zinc. Whereas in the literature *N*-bromosuccinimide (NBS) worked well for the parent *endo*-3-hydroxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene, the hydroxy enamines **20** and **21** only gave complex mixtures of halogenated products, even at −78 °C. In contrast, *N*-iodosuccinimide (NIS) proved to be an efficient and successful halogenating reagent and led to the iodo ethers **22** and **23** in excellent yields of 94% and 89%, respectively (Scheme 4). Attempted hydrogenation[26] of the iodo ether **23** with a variety of catalysts did not lead to any reduction of the enamine double bond. Surprisingly, both the enamine double bond and the α-methylbenzyl group proved inert to hydrogenation even after prolonged reaction times. Use of Pd/C or $Pd(OH)_2$ as catalysts resulted in the cleavage of the allylic carbon−oxygen bond, giving rise to the trans iodo alcohol **24** as the only product. On the contrary, Raney nickel afforded a single product **25** arising from deiodination (Scheme 4). The strategy outlined in the bottom line in Scheme 1, leading to aminocyclopentenols **6**, was abandoned because of the failure of the iodo ether **23** to give the desired reduction.

Single Electron-Transfer Reduction of *N*-Acetyl Enaminones 18 and 19. An attractive alternative conjugated reduction of enones involves the use of alkali and alkaline earth metals in liquid ammonia,[27] which accordingly was attempted for **18** and **19**. Upon treatment of diastereomerically pure **19** with lithium in liquid am-

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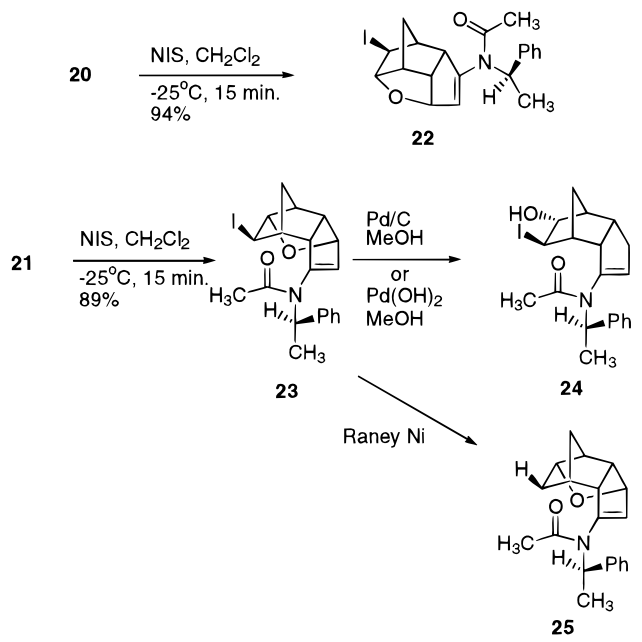
Scheme 4



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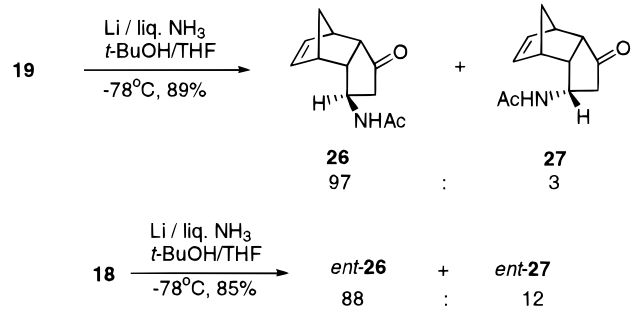


monia as the reducing agent and *t*-BuOH as the proton donor, a diastereomeric mixture of *β*-amino ketones **26** and **27** was obtained in an excellent yield of 89% and with a remarkably high diastereoselectivity (de = 94%)[28] (Scheme 5). This unexpected and facile reduction of the enaminone double bond in **19** along with the concomitant removal of the chiral auxiliary by lithium in liquid ammonia is unprecedented. Even though removal of an α-methylbenzyl group from a tertiary amide using lithium in liquid ammonia has been reported,[29] to our knowledge, this is the first example wherein this method has been used to simultaneously reduce an enaminone double bond with the concurrent removal of an α-methylbenzyl group at nitrogen. Apart from being novel, this method may be general for the synthesis of optically active *β*-amino ketones from enaminones.

Detailed NOESY studies unambiguously revealed the *exo* stereochemistry of the *N*-acetyl amino group in the major diastereomer **26**. The H_5 proton in **26** has a strong NOE with one of the norbornene olefinic protons, presumably H_8, and with H_{4b}, but not with H_{4a} (Figure 4). In addition, the NH proton has a strong NOE with H_{4a} and H_6. It is worth noting that despite the endo face being sterically considerably hindered in **19**, proton donation

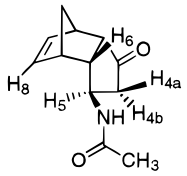
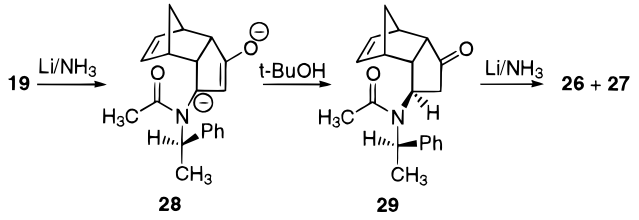


Figure 4.

Scheme 6



at C_5 preferentially occurs from the endo face, thus positioning the *β*-amino group on the exo side of the tricyclodecenyl system. Interestingly, the reduction of the diastereomer **18** gave a similarly high yield of *ent*-**26** and *ent*-**27**, however strikingly, with a considerably lower diastereoselectivity (de = 76%)[28] than observed for the reduction of **19** (de = 94%) (Scheme 5). This difference in the diastereoselectivity shows that the chiral α-methylbenzyl group plays a role in the stereocontrol during the protonation of the intermediate carbanion. As a consequence, it follows that the reduction of the enone moiety precedes the reductive removal of the α-methylbenzyl group (Scheme 6). If true, this sequence of reduction steps also explains the ultimate preferential protonation of the intermediate carbanionic intermediate from the sterically generally less accessible endo face. In the intermediate dianion **28**, the amino functionality containing the bulky α-methylbenzyl group is forced to move away from the endo face of the tricyclic system due to considerable steric interaction with the norbornene unit, thereby promoting protonation from the endo face to form **29**. Furthermore, the nature of the proton donor as well as the order of addition of the reagents seem to play an important role in the course of the reaction. Among the various proton donors tried, viz. water, ammonium chloride, *t*-BuOH, and triphenylmethane, only in the case of *t*-BuOH as the proton donor was the reaction efficient in terms of both yield and diastereoselectivity. With respect to the order of addition: lithium metal must be added to the mixture of the enaminone, *t*-BuOH, THF, and liquid ammonia (see Experimental Section). Changing the order of addition resulted in much lower yields of the desired *β*-amino ketones.

Attempts to separate the diastereomers **26** and **27** by chromatographic methods were not successful; hence, this diastereomeric mixture (de 94%) was subjected to thermolysis in order to bring about the desired [4 + 2] cycloreversion. The retro Diels−Alder reaction proceeded smoothly both under static conditions in refluxing *o*-chlorobenzene (*o*-DCB)[30] as well as under dynamic conditions, applying the flash vacuum thermolytic technique (FVT)[31] at 500 °C and 0.05 mbar to afford (*R*)-(+)-*N*-acetyl-4-aminocyclopent-2-ene-1-one ((+)-**30**), $[\alpha]^{25}_D$ =

(28) The diastereomeric ratios were determined by GC analysis and ^{1}H NMR (300 MHz).

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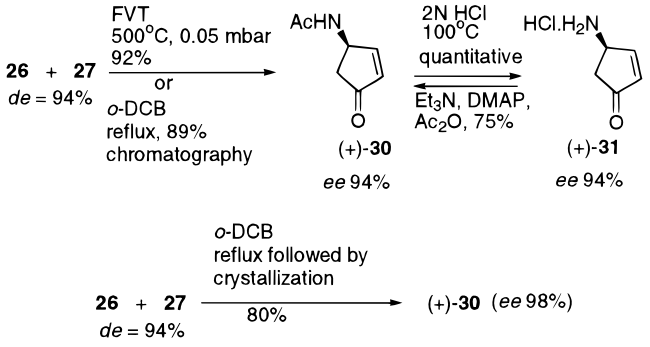
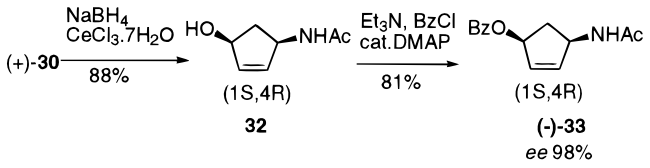
(30) For an example of similar solution thermolysis, see ref 25b.

Scheme 7



Scheme 8



+89° (*c* 0.6, $CHCl_3$), in 89% and 92% yield, respectively (Scheme 7). In both cases, the enantiomeric excess amounted to 94%,[32] showing that under both thermolytic conditions no racemization had occurred. The product (+)-**30** obtained from the FVT experiment was completely chemically pure right away, however, the product obtained from the solution thermolysis needed purification by column chromatography. In contrast to what is generally observed for static thermolysis reactions carried out in boiling *o*-DCB, hardly any decomposition of the produced acetamidocyclopentenone **30** was observed, showing its thermal stability. Even more rewarding is the observation that after thermolysis, cooling of the mixture to room temperature resulted in spontaneous crystallization on standing overnight to give *N*-acetamidocyclopentenone (+)-**30**, $[\alpha]^{20}_D = +93°$ (*c* = 0.5, $CHCl_3$), in 80% yield and with an enriched ee of 98% (Scheme 7).

Removal of the *N*-acetyl group was readily accomplished by hydrolysis of (+)-**30** in 2 N HCl (aq) to yield the hydrochloride salt of (*R*)-(+)-4-aminocyclopent-2-en-1-one ((+)-**31**), $[\alpha]^{22}_D = +61.5°$ (*c* 0.5, MeOH), as a pale yellow solid (Scheme 7). Unfortunately, attempts to recrystallize this ammonium salt did not meet with success. To establish the optical purity of (+)-**31**, it was reconverted to the *N*-acetyl derivative (+)-**30** by treatment with acetic anhydride in the presence of triethylamine (Scheme 7). After purification by column chromatography, the isolated *N*-acetyl compound (+)-**30** had the same optical rotation as the original (+)-**30**, proving that no racemization had occurred either during the hydrolysis or during its reconversion to the *N*-acetyl compound.

To complete the synthesis of *cis*-4-aminocyclopentenol **6**, reduction of the carbonyl group in (+)-**30** was next attempted. While $NaBH_4$ as such gave a mixture of products, stereo- and regioselective reduction was conveniently achieved using $NaBH_4/CeCl_3 \cdot 7H_2O$ (Scheme 8). Even though the reduction proceeded smoothly with high yield (88%), the product alcohol **32** could not be obtained in an entirely pure form due to contamination with a very small amount of some inorganic material. Removal of these impurities was rather troublesome due to the high polarity and therefore high solubility in water of amido alcohol **32**, which did not allow aqueous workup. In addition, overlapping of the signals of H_1 and H_3 at δ 4.69 ppm in the ^1H NMR spectrum of **32** (both in $CDCl_3$ and CD_3OD) rendered it difficult to establish the relative stereochemistry between the hydroxyl and amido functionalities. These problems were readily overcome by converting the alcohol **32** into its benzoate viz. (1*S*,4*R*)-4-*N*-acetylamino-1-benzoyl-cyclopent-2-ene ((−)-**33**) (81% yield), $[\alpha]^{20}_D = -144°$ (*c* 0.5, $CHCl_3$), by treatment with benzoyl chloride in the presence triethylamine and a catalytic amount of DMAP (Scheme 8). The NMR data of the crystalline benzoyl derivative (−)-**33** was consistent with the literature values for structurally similar compounds.[11g] The *cis* stereochemistry between the acetamido and benzoyl groups was unequivocally confirmed by detailed NOESY studies also.

In the same manner, (1*R*,4*S*)-4-*N*-acetylamino-1-benzoyl-cyclopent-2-ene (*ent*-(+)-**33**) was obtained from diastereomer **18**. Cycloreversion of a mixture of *ent*-**26** and *ent*-**27** (de = 76%), obtained by the single electron-transfer reduction of diastereomer **18**, applying both FVT and solution thermolysis, afforded *ent*-(−)-**30**, $[\alpha]^{27}_D = -72.5°$ (*c* 0.49, $CHCl_3$),[32] in 90% yield and with an ee of 76%. Crystallization from *o*-DCB, by allowing the reaction mixture after solution thermolysis to stand at room temperature overnight, led to *ent*-(−)-**30** in 71% yield with an enriched optical purity [ee = 97%; $[\alpha]^{19}_D = -92°$ (*c* 0.48, $CHCl_3$)]. Reduction of *ent*-(−)-**30** using $NaBH_4/CeCl_3 \cdot 7H_2O$ afforded alcohol *ent*-**32** (87% yield), which on benzoylation produced (1*R*,4*S*)-4-*N*-acetylamino-1-benzoyl-cyclopent-2-ene (*ent*-(+)-**33**), $[\alpha]^{20}_D = +142.5°$ (*c* 0.35, $CHCl_3$), in 77% yield and with ee = 97%. The spectral data of *ent*-(+)-**33** were identical to those of (−)-**33**.

Conclusions

We succeeded in an efficient enantioselective synthesis of both enantiomers of 4-*N*-acetylaminocyclopent-2-en-1-one **30** and 4-*N*-acetylamino-1-benzoylcyclopent-2-ene **33**, starting from tricyclo[5.2.1.$0^{2,6}$]decenyl enaminones **14** and **15**. Both enantiomers of **30** and **33** were obtained in excellent overall chemical yields of 71% (three steps) and 50% (five steps) and in almost enantiopure form (ee ≥ 97%). Both the γ-aminocyclopentenones **30**, **31** and aminocyclopentenol derivatives **33** have great potential as building blocks for 5′-norcarbocyclic nucleosides as well as for related antiviral compounds. A key step in our methodology is the concomitant electron-transfer reduction of the enaminone double bond and the reductive elimination of the *N*-α-methylbenzyl group in enaminones **18** and **19**. We have also demonstrated that the regiochemistry of the reduction of N-acylated tricyclic enaminones **18** and **19** can be directed by choosing the appropriate reductive conditions. With 9-BBN, exclusive 1,2-reduction of the C_3-ketone function is observed, whereas selective 1,4-reduction is achieved by electron-transfer reduction with lithium in liquid ammonia in the presence of *t*-BuOH. The generality of this reductive procedure needs to be established for other enaminones.

(31) In our laboratory, this methodology has been successfully applied for the synthesis of a variety of cyclopentanoid natural products. For an illustrative example, see ref 12.

(32) The ee's were determined by using chiral shift reagent $Eu(hfc)_3$ and integrating the separation of the signal due to the β-olefinic proton.

Experimental Section

General Methods. All commercial solvents were distilled according to standard procedures.[33] All commercial chemicals were purchased from Aldrich or Acros and were used as such. Merck Kieselgel 60 F-254 silica gel plates were used for thin-layer chromatography. Column chromatography was carried out with EM Kieselgel 60 silica gel. Unless mentioned otherwise, all ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$. All IR measurements were carried out in $CHCl_3$ solution. Unless stated otherwise, all mass spectra were recorded under EI conditions.

(1*S*,2*R*,6*S*,7*R*,1′*R*)-5-*N*-Acetyl-(*N*-1′-phenylethyl)amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (18). To solution of the enaminone **14**[15] (530 mg, 2 mmol) in dry THF (15 mL) was added sodium hydride (60 mg, 2.5 mmol) at room temperature. After stirring the reaction mixture was stirred for 1 h, acetyl chloride (0.21 mL, 3 mmol) was added dropwise over a period of 10 min. After the reaction mixture was stirred for another 2 h at room temperature, it was carefully quenched with water and extracted with CH_2Cl_2. The organic layer was then washed with water, dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (hexane/EtOAc 1:1) to afford **18** (522 mg, 85%) as a viscous yellow liquid: $[\alpha]^{20}_D = -345°$ (*c* 1.25, $CHCl_3$); IR 1690, 1680, 1670 cm^{-1}; ^{1}H NMR δ 7.21−7.40 (m, 5H), 6.06 (dd, J = 5.5, 2.8 Hz, 1H), 5.77−5.88 (m, 2H), 5.26 (s, 1H), 3.92 (m, 1H), 3.15 (broad s, 1H), 2.90 (m, 1H), 2.45 (broad s, 1H), 2.28 (s, 3H), 1.70 (d, J = 7.1 Hz, 3H), 1.65 (d, J = 8.5 Hz, 1H), 1.47 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 206.4, 171.9, 171.1, 140.2, 133.8, 132.1, 128.6, 127.3, 125.7, 123.8, 54.3, 52.5, 50.6, 49.4, 44.1, 44.0, 24.4, 16.1; MS *m*/*z* 307 (M$^+$), 279, 264, 199; HRMS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1573.

(1*R*,2*S*,6*R*,7*S*,1′*R*)-5-N−Acetyl-(*N*-1′-phenylethyl)amino-*endo*-tricyclo[5.2.1.0.^{2,6}]deca-4,8-dien-3-one (19). In a similar way as described for the synthesis of **18** from **14**, the diastereomeric enaminone **15** afforded the *N*-acetyl derivative **19** in 89% yield as a yellow solid: mp 139−140 °C; $[\alpha]^{21}_D$ = +447° (*c* 0.45, $CHCl_3$); IR 1690, 1680, 1670 cm^{-1}; ^{1}H NMR δ 7.21−7.40 (m, 5H), 6.07 (dd, J = 5.6, 2.9 Hz, 1H), 5.89 (dd, J = 5.6, 2.9 Hz, 1H), 5.63 (q, J = 7.0 Hz, 1H), 5.44 (s, 1H), 3.71 (dd, J = 5.9, 4.2 Hz, 1H), 3.18 (broad s, 1H), 3.04 (broad s, 1H), 2.84 (dd, J = 5.9, 4.8 Hz, 1H), 2.17 (s, 3H), 1.82 (d, J = 7.0 Hz, 3H) 1.76 (d, J = 8.5 Hz, 1H), 1.58 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 206.2, 173.0, 170.8, 138.9, 134.1, 131.7, 128.3, 127.2, 126.1, 123.4, 55.5, 52.2, 50.8, 49.0, 44.6, 43.8, 24.6, 17.5; MS *m*/*z* 307 (M$^+$), 279, 264, 237, 199, 105, 43 HRMS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1573.

(1*S*,2*R*,3*R*,6*S*,7*R*,1′*R*)-5-*N*-Acetyl-(*N*-1′-phenylethyl)amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol (20). To a flame-dried flask cooled under argon was added enaminone **18** (614 mg, 2 mmol), which was dissolved in dry THF (6 mL). The reaction mixture was cooled to 0 °C. A 0.5 M solution of 9-BBN in THF (6 mL, 3 mmol) was injected dropwise. The reaction mixture was stirred at 0 °C for 4 h and then at room temperature for 2 h. Excess 9-BBN was quenched by adding MeOH. The reaction mixture was then concentrated in a rotary evaporator. The resulting residue was dissolved in EtOAc, and ethanolamine was added. The precipitate formed was separated. The EtOAc layer was concentrated and the product purified by column chromatography (hexane/EtOAc 1:3) to afford the alcohol **20** (512 mg, 83%) as a colorless viscous liquid: IR 3300, 1630 cm^{-1}; ^{1}H NMR δ 7.20−7.40 (m, 5H), 6.23 (dd, J = 5.4, 2.8 Hz, 1H), 6.02 (q, J = 7.4 Hz, 1H), 5.84 (dd, J = 5.6, 3.1 Hz, 1H), 5.31 (d, J = 1.8 Hz, 1H), 4.69 (m, 1H), 3.00-(m, 2H), 2.87 (broad s, 1H), 2.17 (s, 3H), 1.80 (broad s, 1H), 1.53 (d, J = 7.2 Hz, 3H), 1.36 (d, J = 8.2 Hz, 1H), 1.29 (d, J = 9.0 Hz, 1H), 1.12 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 170.3, 145.4, 142.1, 134.4, 134.2, 130.9, 128.1, 127.1, 126.9, 72.5, 54.6, 52.9, 50.1, 47.3, 46.3, 44.4, 23.1, 16.1; MS *m*/*z* 309 (M$^+$), 227, 204, 187, 139; HRMS calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1729.

(33) Perrin, D. D.; Armarego, W. L. F. In *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(1*R*,2*S*,3*S*,6*R*,7*S*,1′*R*)-5-*N*-Acetyl-(*N*-1′-phenylethyl)amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ol (21). In the same manner as described for the synthesis of alcohol **20**, the *N*-acetyl enaminone **19** underwent reduction with 9-BBN to give alcohol **21** in 92% yield as a colorless viscous liquid: IR 3300, 1630 cm^{-1}; ^{1}H NMR δ 7.18−7.38 (m, 5H), 6.29 (dd, J = 5.6, 2.0 Hz, 1H), 5.93 (dd, J = 5.6, 3.1 Hz, 1H), 5.60 (q, J = 7.1 Hz, 1H), 5.22 (s, 1H), 4.45 (t, J = 7.1 Hz, 1H), 3.18 (dd, J = 6.8, 3.3 Hz, 1H), 2.90 (m, 3H), 2.12 (s, 3H), 1.74 (d, J = 7.1 Hz, 3H), 1.60 (d, J = 8.3 Hz, 1H), 1.40 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 170.0, 146.1, 140.0, 134.7, 134.2, 131.5, 127.9, 127.3, 126.9, 72.5, 54.7, 53.6, 52.9, 47.0, 44.3, 23.2, 17.8; MS *m*/*z* 309 (M$^+$), 227, 204, 187, 139; HRMS calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1729.

(1*S*,2*R*,3*S*,6*S*,8*R*,9*R*,10*R*,1′*R*)-4-*N*-Acetyl-(*N*-1′-phenylethyl)amino-9-iodo-7-oxatetracyclo[6.3.0.0^{2,6}.0^{3,10}]undec-4-ene (23). To a solution of the alcohol **21** (192 mg, 0.62 mmol) in CH_2Cl_2 (3 mL) cooled to −25 °C in a dry ice−acetone bath was added *N*-iodosuccinimide (168 mg, 0.75 mmol). After 10 min, when TLC showed the absence of starting material, the reaction was stopped, CH_2Cl_2 was removed, and the residue was purified by column chromatography (hexane/EtOAc 1:1) to give iodo ether **23** (239 mg, 89%) as a colorless viscous liquid: $[\alpha]^{19}_D = -10°$ (*c* 0.78, $CHCl_3$); IR 1640, 1620 cm^{-1}; ^{1}H NMR δ 7.20−7.40 (m, 5H), 5.71−5.80 (m, 2H), 4.81 (d, J = 5.0 Hz, 1H), 4.55 (dd, J = 6.0, 2.9 Hz, 1H), 3.89 (d, J = 2.5 Hz, 1H), 3.05 (dt, J = 8.8, 5.7 Hz, 1H), 2.80 (dd, J = 8.8, 3.8 Hz, 1H), 2.56 (m, 1H), 2.35 (d, J = 11.0 Hz, 1H), 2.13 (s, 3H), 1.86 (d, J = 11.0 Hz), 1.65 (d, J = 7.1 Hz); ^{13}C NMR δ 169.8, 145.9, 140.5, 131.7, 128.7, 127.2, 126.8, 92.1, 82.1, 54.1, 52.9, 49.9, 48.8, 47.4, 41.8, 32.8, 23.1, 17.5; MS *m*/*z* 435 (M$^+$), 392, 331, 308, 204, 105; HRMS calcd for $C_{20}H_{22}NO_2I$ 435.0695, found 435.0698.

(1*R*,2*S*,6*R*,7*S*,8*R*,9*R*,1′*R*)-3-*N*-Acetyl-(*N*-1′-phenylethyl)-amino-9-iodo-*endo*-tricyclo[5.2.1.0^{2,6}]dec-3-en-8-ol (24). To a solution of the iodo ether **23** (43.5 mg, 0.1 mmol) in MeOH (3 mL) was added a catalytic amount of Pd/C or $Pd(OH)_2$ and the reaction mixture subjected to hydrogenation at room temperature and atmospheric pressure. The progress of the reaction was monitored by TLC. When TLC indicated the disappearance of the starting material, hydrogenation was stopped. The catalyst was filtered and the solvent removed. Purification of the product by column chromatography (hexane/EtOAc 1:1) afforded trans iodo alcohol **24** (24 mg, 52%) as a sticky solid: $[\alpha]^{18}_D = +110°$ (*c* 0.25, $CHCl_3$); IR 3500, 1640, 1620 cm^{-1}; ^{1}H NMR δ 7.19−7.40 (m, 5H), 5.50 (d, J = 1.3 Hz, 1H), 5.31 (q, J = 7.2 Hz, 1H), 4.79 (q, J = 4.3 Hz, 1H), 4.03 (t, J = 3.4 Hz, 1H), 3.11 (m, 2H), 2.67 (m, 2H), 2.00−2.38 (m, 7H), 1.75 (d, J = 7.1 Hz, 1H), 1.50−1.56 (m, 2H); ^{13}C NMR δ 170.4, 140.6, 140.5, 130.8, 128.2, 126.8, 89.1, 55.5, 55.2, 52.2, 46.6, 40.2, 39.2, 32.0, 29.3, 23.3, 18.1; MS *m*/*z* 437 (M$^+$), 394, 332, 105; HRMS calcd for $C_{20}H_{24}NO_2I$ 437.0852, found 437.0850.

(1*S*,2*R*,3*R*,6*S*,8*S*,10*S*,1′*R*)-4-*N*-Acetyl-(*N*-1′-phenylethyl)amino-7-oxatetracyclo[6.3.0.0^{2,6}.0^{3,10}]undec-4-ene (25). The reduction procedure was similar to that of the previous experiment. Instead of Pd/C or $Pd(OH)_2$, a catalytic amount of Raney nickel was employed as the catalyst. The reaction resulted in the formation of deiodinated product **25** (100%) as a white solid: mp 85−86 °C; $[\alpha]^{20}_D = +49.2°$ (*c* 0.32 $CHCl_3$); IR 1640, 1620 cm^{-1}; ^{1}H NMR δ 7.20−7.35 (m, 5H), 5.64−5.79 (m, 2H), 4.60 (dd, J = 6.1, 2.8 Hz, 1H), 4.41 (dd, J = 7.5, 5.1 Hz, 1H), 2.99 (m, 1H), 2.73 (dd, J = 7.6, 3.3 Hz, 1H), 2.53 (t, J = 5.0 Hz, 1H), 2.13 (s, 3H), 1.68 (d, J = 7.1 Hz, 3H), 1.25−1.61 (m, 5H); ^{13}C NMR δ 169.8, 147.2, 140.8, 131.0, 128.0, 127.3, 127.0, 81.8, 54.8, 52.8, 51.0, 47.0, 42.2, 39.2, 36.5, 23.1, 17.3; MS *m*/*z* 309(M$^+$), 266, 206, 105; HRMS calcd for $C_{20}H_{23}NO_2$ 309.17288, found 309.17290.

(1*R*,2*S*,5*R*,6*R*,7*S*)-5-*N*-Acetylamino-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3-one (26) and (1*R*,2*S*,5*S*,6*R*,7*S*)-5-N−Acetylamino-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3-one (27). A 500 mL three-necked flask containing an ammonia inlet, a dropping funnel, and a KOH guard tube, cooled to −78 °C (dry ice−acetone bath), was charged with liquid ammonia (150 mL). *N*-Acetyl enaminone **19** (921 mg, 3 mmol) dissolved in THF (3 mL) was added dropwise followed by the addition of *t*-BuOH

(888 mg, 12 mmol) in THF (2 mL). Freshly cut fine pieces of lithium (168 mg, 24 mmol) were added to this mixture under vigorous stirring. After some time (5−10 min), the reaction mixture became completely blue. The reaction mixture was stirred at −78 °C until all the blue color had disappeared. The cooling bath was then removed and the ammonia evaporated using a water bath. The residue was dissolved in a minimum amount of water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification over column chromatography (EtOAc/MeOH 20:1) afforded an inseparable diastereomeric mixture of *β*-amino ketones **26** and **27** (550 mg, 89%) as a colorless viscous oil. The diastereomeric ratio was 97:3 as determined by GC as well as by the ^{1}H NMR spectrum: $[\alpha]^{25}_D = +145.5°$ (*c* 0.95, $CHCl_3$); IR 3420, 1730, 1660 cm^{-1}; ^{1}H NMR *δ* (for major diastereomer **26**) 6.26 (m, 2H), 6.12 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.86 (m, 1H), 3.22 (m, 2H), 3.05 (m, 1H), 2.86 (m, 1H), 2.42 (dd, *J* = 19.1, 9.0 Hz, 1H), 2.13 (ddd, *J* = 19.1, 5.2, 1.6 Hz, 1H), 1.99 (s, 3H), 1.57 (d, *J* = 8.3 Hz, 1H), 1.40 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (*δ* for major diastereomer **26**) *δ* 218.6, 169.5, 136.2, 134.7, 54.9, 52.1, 50.9, 48.55, 48.51, 46.9, 46.6, 23.1; MS *m*/*z* 205 (M^+), 177, 147, 140, 66; HRMS calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1104.

(1*S*,2*R*,5*S*,6*S*,7*R*)-5-*N*-Acetylamino-*endo*-tricyclo-[5.2.1.0^{2,6}]dec-8-ene-3-one (*ent*-26) and (1*S*,2*R*,5*R*,6*S*,7*R*)-5-*N*-Acetylamino-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3-one (*ent*-27). Following the same procedure as above, a diastereomeric mixture of *ent*-**26** and *ent*-**27** was obtained from the enaminone **20** in 85% yield and with a diastereomeric ratio of 88:12. The spectral data of the major enantiomer *ent*-**26** were identical with those of **26**: $[\alpha]^{23}_D = -137.6°$ (*c* 1.0, $CHCl_3$).

(*R*)-(+)-4-*N*-Acetylaminocyclopent-2-ene-1-one 30. By Flash Vacuum Thermolysis. The diastereomeric mixture of *β*-amino ketones **26** and **27** (92 mg, 0.45 mmol; de = 94%) was subjected to flash vacuum thermolysis at 500 °C and 0.05 mbar. The product was collected on a coldfinger cooled with dry ice/acetone. When all the starting material had been consumed, the thermolysis was stopped. The product collected on the coldfinger was removed by dissolving it in CH_2Cl_2. Removal of the solvent gave pure (+)-**30** in 92% yield (*ee* 94%) as a white solid: mp 107−108 °C; $[\alpha]^{25}_D = +89°$ (*c* 0.61, $CHCl_3$); IR 3420, 1720, 1680, 1670 cm^{-1}; ^{1}H NMR *δ* 7.55 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.38 (bs, 1H), 6.23 (dd, *J* = 5.6, 1.7 Hz, 1H), 5.24 (m, 1H), 2.84 (dd, *J* = 18.7, 6.8 Hz, 1H), 2.16 (dd, *J* = 18.8, 2.5 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR *δ* 206.7, 169.9, 162.2, 135.2., 49.6, 41.7, 23.0; HRMS calcd for $C_7H_9NO_2$ 139.06333, found 139.06336. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.66; H, 6.30; N, 9.88.

By Solution Thermolysis. A solution of the *β*-amino ketones **26** and **27** (205 mg, 1 mmol; de 94%) in *o*-dichlorobenzene (5 mL) was refluxed in an oil bath at 185 °C. The progress of the reaction was monitored by TLC. When TLC indicated the absence of starting material, refluxing was stopped. Removal of the solvent and purification by column chromatography (EtOAc/MeOH 20:1) afforded (+)-**30** in 89% yield and with an ee of 94%, $[\alpha]^{25}_D = +89°$ (*c* 1, $CHCl_3$). On the other hand, cooling the reaction mixture overnight led to crystallization yielding (+)-**30** in 80% yield and with an enriched ee of 98%, $[\alpha]^{20}_D = +93°$ (*c* 0.48, $CHCl_3$).

(*S*)-(−)-4-*N*-Acetylaminocyclopent-2-en-1-one (*ent*-30). (*S*)-(−)-4-(*N*)-Acetylaminocyclopent-2-en-1-one (*ent*-**30**) was obtained from a diastereomeric mixture of *ent*-**26** and *ent*-**27** (de 76%), both by FVT as well as solution thermolysis. Flash vacuum thermolysis (500 °C, 0.05 mbar) afforded *ent*-**30** in 90% yield and with an ee of 76%, $[\alpha]^{27}_D = -72.5°$ (*c* 0.49, $CHCl_3$), while solution thermolysis in *o*-dichlorobenzene (refluxing at 185 °C) followed by crystallization from the reaction mixture gave *ent*-**30** in 71% yield and with an enriched ee of 97%, $[\alpha]^{19}_D = -92°$ (*c* 0.48, $CHCl_3$).

(*R*)-(+)-4-Aminocyclopent-2-en-1-one Hydrochloride (31). A solution of (+)-**30** in 2 N HCl (3 mL) was heated at 100 °C for 3 h. The reaction mixture was then cooled and the solution evaporated to dryness in a rotary evaporator to yield (*R*)-(+)-4-aminocyclopent-2-en-1-one hydrochloride **31** as a pale yellow solid in quantitative yield. The solid did not melt but decomposed above 170 °C: $[\alpha]^{20}_D = +61.5°$ (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) *δ* 7.70 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.50 (dd, *J* = 5.7, 1.7 Hz, 1H), 4.58 (m, 1H), 2.86 (dd, *J* = 18.7, 6.8 Hz, 1H), 2.35 (dd, *J* = 18.7, 2.4 Hz, 1H); ^{13}C NMR (CD_3OD) *δ* 205.8, 158.8, 139.2, 51.6, 39.7; MS *m*/*z* 97(M^+ − HCl), 69, 38($H^{37}Cl$), 36($H^{35}Cl$); FAB (*m*-nitrobenzyl alcohol) 98 (M^+ − Cl), 81; HRMS calcd for C_5H_7NO (M^+− HCl) 97.052 76, found 97.052 87.

(1*S*,4*R*)-4-*N*-Acetylaminocyclopent-2-en-1-ol (32) and Its Benzoyl Derivative (33). To a solution of **30** (125 mg, 0.9 mmol) in MeOH (3 mL) was added $CeCl_3 \cdot 7H_2O$ (336 mg, 0.9 mmol) and the mixture stirred at room temperature for 1 h. The reaction mixture was then cooled to −78 °C, and $NaBH_4$ (76 mg, 2 mmol) was added as such in one portion. Progress of the reaction was monitored by TLC. When TLC indicated the complete consumption of the starting material, the reaction was stopped, the solvent removed, and the product immediately purified by column chromatography (EtOAc/MeOH 20:1) to give **32** (108 mg, 88%) as a viscous oil: IR 3420, 3360, 1670, 1650 cm^{-1}; ^{1}H NMR (CD_3OD) *δ* 5.94 (dt, *J* = 7.4, 1.8 Hz, 1H), 5.80 (dt, *J* = 7.1, 1.6 Hz, 1H), 4.69 (m, 2H), 2.71 (dt, *J* = 13.5, 7.5 Hz, 1H), 1.92 (s, 3H), 1.39 (dt, *J* = 13.5, 5.5 Hz, 1H); ^{13}C NMR *δ* 172.5, 137.5, 134.3, 75.7, 54.5, 41.9, 22.6; MS *m*/*z* 141(M^+), 124, 98; HRMS calcd for $C_7H_{11}NO_2$ 141.078 98, found 141.078 93.

Since the product obtained was not entirely pure, it was immediately benzoylated. To a solution of alcohol **32** (108 mg, 0.79 mmol) in CH_2Cl_2 (5 mL), cooled to 0 °C in an ice bath were added Et_3N (0.25 mL, 2 mmol) and DMAP (10 mg). After the reaction mixture was stirred for 15 min, benzoyl chloride (0.13 mL, 1 mmol) was added. After 2 h, TLC showed the reaction to be complete, and it was stopped. The solvent was removed and the product purified by column chromatography (hexane/EtOAc 1:1) to yield **33** (156 mg, 81%) as a white crystalline material: mp 138 °C, ee 98%; $[\alpha]^{20}_D = -144°$ (*c* 0.5, $CHCl_3$); IR 3420, 1710, 1670 cm^{-1}; ^{1}H NMR *δ* 8.02 (m, 2H), 7.40−7.60 (m, 3H), 6.00−6.18 (m, 2H), 5.79 (m, 1H), 5.65 (m, 1H), 5.04 (m, 1H), 2.98 (dt, *J* = 14.6, 7.7 Hz, 1H); 2.00 (s, 3H), 1.69 (dt, *J* = 14.6, 4.1 Hz, 1H); ^{13}C NMR *δ* 169.2, 166.0, 136.7, 133.0, 132.6, 130.1, 129.5, 128.3, 78.2, 53.0, 38.4, 23.3; MS(CI) *m*/*z* 246 (MH^+, very weak), 187, 152, 124, 105; HRMS calcd for $C_{12}H_{11}O_2$ (M^+ − NHAc) 187.0759, found 187.0758. Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.10; N, 5.71. Found: C, 68.08; H, 6.05; N, 5.70.

(1*R*,4*S*)-4-*N*-Acetylamino-1-benzoylcyclopent-2-ene (*ent*-33). Using the same procedure as above and starting from *ent*-**30** (ee = 97%), *ent*-**33** was obtained in 77% yield and with an ee of 97%: $[\alpha]^{20}_D = +142.5°$ (*c* 0.35, $CHCl_3$).

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **18**−**20**, **23**, **25**, (**26** + **27**), (*ent*-**26** + *ent*-**27**), **30**, **31**, **33**, ^{13}C NMR spectrum for compound **24**, and 2D-NOESY spectra for compounds (**26** + **27**) and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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