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Preparation and Cycloaddition Reactions of Enantiopure 2-(*N*-Acylamino)-1,3-dienes for the Synthesis of Octahydroquinoline Derivatives

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Stille, Suzuki−Miyaura, and Sonogashira cross-coupling reactions were carried out with a glutarimide-derived vinyl phosphate, bearing a chiral auxiliary on the N atom, to prepare enantiopure 2-(*N*-acylamino)-1,3-dienes as partners in Diels−Alder reactions. The cycloadditions were performed with various dienophiles under thermal conditions, with or without Lewis acids. With maleimides, the preferential formation of endo cycloadducts was observed, whereas with acrylamides the exo approach prevailed. Furthermore, in the latter case, 6-substitued octahydroquinolinones were obtained in accordance with the predicted regioselectivity. Since diastereopure compounds were in all cases obtained either by chromatography or by crystallization, and because of the easy access to a variety of boronic acids, to be used in the coupling step, this methodology is useful for the short synthesis of differently substituted, enantiopure octahydroquinolinones amenable to further transformation into decahydroquinolines possessing interesting biological activities.

Introduction

In recent years, the Pd-catalyzed cross-coupling reactions of lactam-derived vinyl triflates[1] and phosphates[2] **1** and **2** (Figure 1) have gained increasing importance in the synthesis of heterocyclic compounds.[3] To this end, an effective strategy involves reacting **1** with tributyl(vinyl)-tin in order to obtain coupling products such as **3** (Figure 1) containing a 2-(*N*-acylamino)-1,3-diene moiety.[3h] These are then used for [4 + 2] cycloadditions with various dienophiles to prepare octahydroquinolines[3h,4] as intermediates in the synthesis of decahydroquinolines.[5] Our interest in Pd-catalyzed cross-coupling reactions[1a,b,3a] has led us to undertake a research on the use of an imide-derived vinyl phosphate of type **4** (Figure 1) that bears a simple and inexpensive chiral auxiliary on the N atom, for the preparation of enantiopure 2-(*N*-acylamino)-1,3-dienes **5** to be used as partners in cycloaddition reactions for the synthesis of octahydroquinoline derivatives. Further interest in this study was stimulated by the fact that 2-(*N*-acylamino)-1,3-dienes have been very rarely used

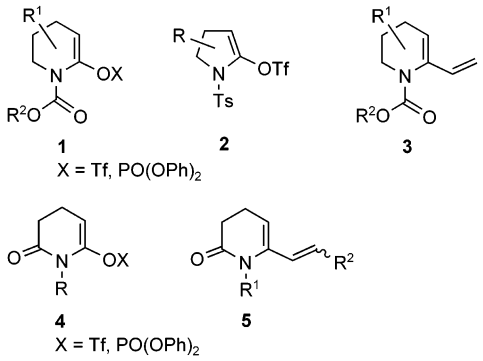

FIGURE 1.

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(4) A similar approach to the synthesis of enantiopure octahydroquinolines is based on Diels−Alder reactions of *N*-acyl 5-vinyl-2,3-dihydro-4-pyridones prepared by Stille coupling reaction of the corresponding 5-iodo substituted pyridones with tributyl(vinyl)tin. Kuethe, J. T.; Brooks, C. A.; Comins, D. L. *Org. Lett*. **2003**, *5*, 321−323.

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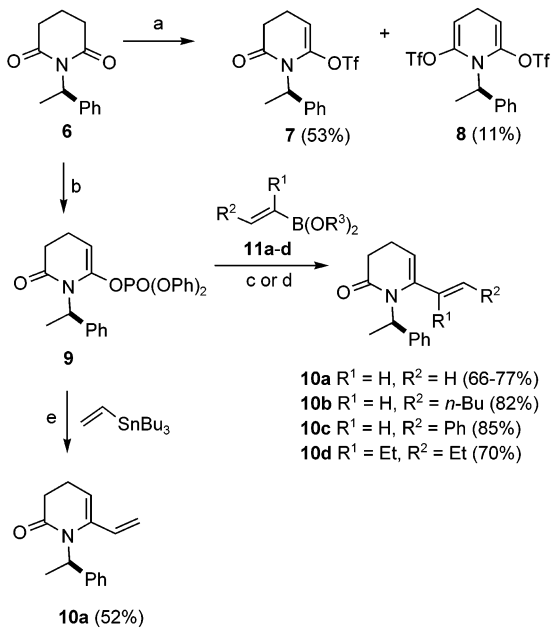
in cycloaddition reactions[3h,6] and that, therefore, little is known about their reactivity. For example, a strikingly anomalous regiochemical preference, in contrast to the predictions based on HOMO diene−LUMO dienophile interactions, has been observed in the cycloadditions of dienes **3** with acrylates and other dienophiles.[3h]

Imides are good candidates for the generation of type **4** vinyl triflates or phosphates (Figure 1) since the second, unreacted carbonyl group can stabilize the structure in the same way as the electron-withdrawing N substituent[1c] present in the analogous compounds **1** and **2**. That of an intramolecular Heck reaction leading to racemic cytisine is the only application example of these imide derivatives in Pd-catalyzed reactions,[7] whereas, to our knowledge, cross-coupling processes such as Stille, Suzuki−Miyaura, and Sonogashira reactions involving **4** have never been described.

Results and Discussion

For this study, we chose enantiopure (*R*)-(+)-glutarimide **6** (Scheme 1) as the starting material for the generation of the corresponding vinyl phosphate and triflate derivatives. Imide **6** was prepared starting from commercially available glutaric anhydride and (*R*)-(+)-1-phenylethylamine through a modification of a reported procedure.[8] After a series of failed attempts to quantitatively prepare triflate **7**, with the concurrent formation of bis-triflate **8** being in some cases observed, we turned to the use of cheaper vinyl phosphate **9** for carrying out the coupling reactions (Scheme 1). Imide **6** was quantitatively converted into vinyl phosphate **9** by treatment with LHMDS at 0 °C in THF, followed by addition of $(PhO)_2P(O)Cl$ at −78 °C. Attempts at obtaining pure **9** by chromatography on neutral alumina were unfruitful, since they caused partial degradation to the starting imide. However, we found that **9** can be conveniently used in the cross-coupling reactions as a crude material, although within a few days after its preparation, as it tends to decompose even when stored at 4 °C. Coupling carried out with tributyl(vinyl)tin under standard Stille conditions (Scheme 1) afforded diene **10a** in 52% yield. The introduction of the unsubstituted vinyl moiety was also achieved through a Suzuki−Miyaura coupling with commercially available vinylboronic acid dibutyl ester **11a** ($R^1 = R^2 = H$, $R^3 = n$-Bu). Since competing and sometimes prevailing Heck reactions have been reported for vinylboronic esters,[9] we thought that a quantitative quaternization of the boron atom prior reacting **11a** with **9** under Pd catalysis would decrease the extent of this unwanted reaction.[10] Thus, **11a** was treated with 1 equiv of MeONa in THF and the resulting solution used for the coupling with **9** in the presence of 5% $(Ph_3P)_4Pd$ as a catalyst at 40 °C in THF. The reaction was complete after 2 h and afforded pure **10a** in 66% yield after chromatography. The Heck product was not observed by ^1H NMR analysis of the crude reaction mixture. Even better results were obtained by carrying out the reaction under conditions already experimented for the coupling of lactam-derived vinyl triflates with boronic acids,[1a] i.e., with 5% $(Ph_3P)_2PdCl_2$ in THF and aqueous 2 M Na_2CO_3 as a base, providing **10a** in 77% yield.

SCHEME 1[a]



[a] Key: (a) KHMDS, THF, −78 °C, 1 h; then $PhNTf_2$, − 78 °C to rt, 1 h; (b) LHMDS, THF, 0 °C to rt, 1 h; then $(PhO)_2P(O)Cl$, −78 °C to rt, 1.5 h; (c) 5% $(Ph_3P)_4Pd$, MeONa, THF, 40 °C; (d) 5% $(Ph_3P)_2PdCl_2$, THF, 2 M Na_2CO_3, 40 °C; (e) 4% $(Ph_3P)_4Pd$, LiCl (10 equiv), THF, reflux, 4 h.

These conditions were then applied to the coupling of **9** with boronic acids **11b**,**c** ($R^3 = H$) and 2-[(*Z*)-1-ethylbut-1-enyl]benzo-1,3,2-dioxaborole **11d** (Scheme 1), affording the corresponding coupling products **10b**−**d** in 70−85% yield. All these coupling products proved stable, with the exception of **10c** which tends to decompose and therefore must be used for the subsequent reactions within a few days after its preparation.

Coupling of **9** with boronic acid derivatives **11b**,**c** gave the corresponding dienes **10b**,**c** with the external double bond having *E* stereochemistry. The corresponding *Z*

(5) The importance of these compounds arises from the presence of the decahydroquinoline ring in several natural alkaloids isolated from, e.g., the tunicate *Clavelina lepadiformis*, predatory flatworm *Prosthecereaeus villatus*, Lycopodium club mosses, skin of Dendrobates amphibians, and myrmicine ants. These and several, related synthetic molecules exert diverse biological activities which depend on the type and degree of substitution and ring fusion. See, for example: Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod*. **1999**, *62*, 5−21. Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43, pp 185−288. Daly, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 141−169. Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem*. **2001**, *66*, 3338−3347 and referenced therein. Morita, H.; Hirasawa, Y.; Yoshida, N.; Kobayashi, J. *Tetrahedron Lett*. **2001**, *42*, 4199−4201 and references therein.

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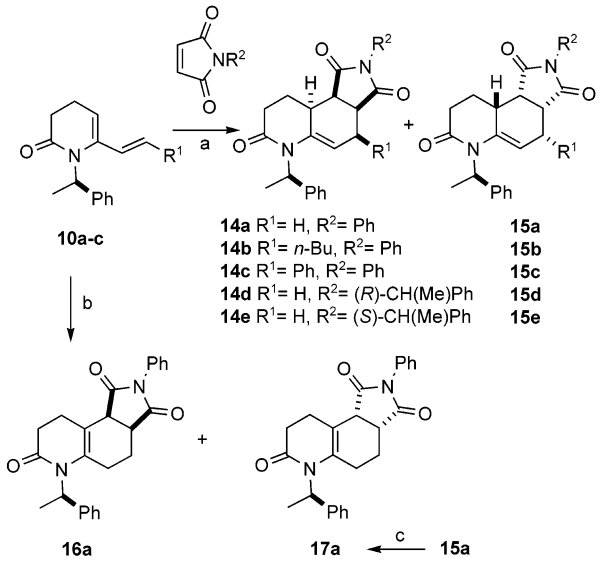
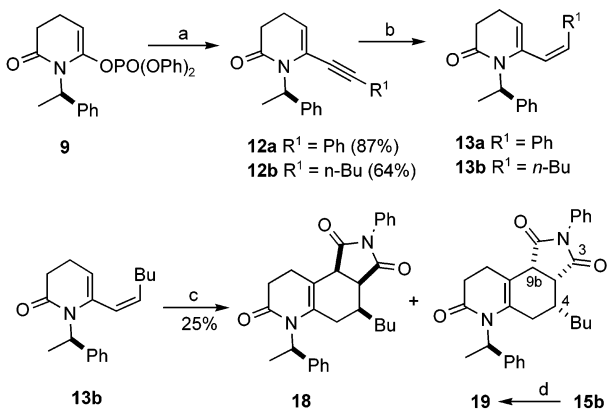
(10) This should increase the rate of the transmetalation step. Molander has recently reported on the use of potassium vinyltrifluoroborate as a useful reagent for introducing a vinyl moiety by Pd-catalyzed reaction with aryl halides and triflates without competing Heck reaction. Molander, G. A.; Rivero, M. R. *Org. Lett*. **2002**, *4*, 107−109.

SCHEME 2[a]



[a] Key: (a) see Table 1 for conditions; (b) *N*-phenylmaleimide, $TiCl_4$, CH_2Cl_2, −78 °C, 15 min; (c) $TiCl_4$, CH_2Cl_2, −78 °C, 15 min.

SCHEME 3[a]



[a] Key: (a) 5% $(Ph_3P)_2PdCl_2$, 10% CuI, 1-alkyne, TEA−$CHCl_3$ 3:1, 1 h, 50 °C; (b) 5% Pd/$CaCO_3$−Pb, H_2(g), EtOH, rt; (c) *N*-phenylmaleimide, toluene, 100 °C, 24 h; (d) $TiCl_4$, CH_2Cl_2, −78 °C.

compounds could be obtained by Sonogashira couplings of **9** with 1-hexyne and phenylacetylene, followed by partial hydrogenation of the triple bond (Scheme 3). The couplings furnished **12a** and **12b** in 87 and 64% yield, respectively, but the partial hydrogenation over Lindlar catalyst proved quite troublesome as dienes **13** could never be obtained as the only hydrogenation products. Under the best conditions (5% Pd/$CaCO_3$ + Pb, in EtOH), compounds **13a** and **13b** were obtained in 60 and 70% yield, respectively, as mixtures containing the products bearing a fully hydrogenated side chain.

In the initial stage of this study, a first series of cycloadditions was carried out with the symmetrical dienophile *N*-phenylmaleimide in order to avoid the formation of regioisomeric mixtures (Scheme 2). After a series of experiments (Table 1, entries 1−4), we eventually found that the reaction of **10a** with *N*-phenylmaleimide is best carried out at low temperature (−18 °C) and by increasing the concentration of the diene up to 2.1 M (entry 5). Under these conditions, the cycloaddition was complete in 3 days, providing the highest endo/exo product ratio (12:1). The mixture of endo products **14a** and **15a**, in which **15a** was prevailing (60% de), was obtained in 90% yield after chromatography. Although the reaction did not occur with high facial selectivity, the major diastereomer **15a** could be obtained in pure form and good yield (52%) by crystallization from an EtOAc/cyclohexane mixture.

X-ray analysis[11] of the crystals (see the Supporting Information) allowed us to assign the absolute configuration of the newly created stereocenters and ascertain that the dienophile preferentially approached the face of diene **10a** opposite to the phenyl group of the auxiliary, according to a model in which the smallest substituent of the auxiliary (the H atom) points toward the external double bond.[8,12]

Another reaction of diene **10a** with *N*-phenylmaleimide was carried out in the presence of 1 equiv of $TiCl_4$ at −78 °C (Scheme 2). The reaction was complete in 15 min, but provided a mixture of diastereomers **16a** and **17a** (not separated by chromatography or crystallization) in a low ratio (33% de), in which migration of the double bond had occurred. The structural assignment to the major diastereomer was possible as treatment of pure **15a** with $TiCl_4$ at − 78 °C for 15 min leads to almost complete isomerization to **17a** (95% conversion by ^{1}H NMR analysis).

The reaction of *N*-phenylmaleimide with a high concentration of the dienes **10b** and **10c** was carried out as described above at −18 °C (entries 8 and 10), yielding in both cases separable mixtures of endo/exo products in a 13:1 ratio and major diastereomers **15b** and **15c** with a 74% de value. Diasteropure **15b** and **15c** were obtained in good yields (61−64%) by crystallization from EtOAc/cyclohexane. X-ray analyses[11] of the crystals (see the Supporting Information) were again consistent with the model proposed above for the approach of the dienophile. Finally, diene **10d** failed to react with *N*-phenylmaleimide even in refluxing toluene, presumably because of the strain between the chiral auxiliary and one of the ethyl residues, which prevents the diene from assuming the required s-cis conformation.

In the attempt at increasing the facial selectivity by double stereodifferentiation, **10a** was reacted with both enantiomers of commercial *N*-(1-phenylethyl)maleimide (Scheme 2) under the conditions of entry 3 reported in Table 1. However, not only did the de values not increase compared with the cycloaddition with *N*-phenylmaleimide (Table 1, entry 3), but the sterically more demanding N substituent of the imide amplified the exo approach. In fact, the reaction with the *R* maleimide produced a mixture of separable endo and exo products in a 2.3:1 ratio, with the predominant isomer **15d** (structural assignment tentative, based on comparison of the ^{1}H NMR spectra of **15d** and **15a**) having a 46% de value.

(11) The X-ray CIF files for all structures have been deposited at the Cambridge Crystallographic Data Centre and allocated with the deposition numbers CCDC 200006 for compound **15a**, CCDC 200008 for compound **15b**, CCDC 200007 for compound **15c**, CCDC 201406 for compound **20b**, CCDC 208282 for **21d**.

(12) A Monte Carlo conformational search did not rule out, however, other possible conformations stabilized by π-stacking between the phenyl group of the auxiliary and the external double bond, which further complicate the interpretation of the stereochemical outcome.

TABLE 1. Cycloadditions of 10a−c with *N*-Phenylmaleimide

entry	R	conditions	time (h)	endo/exo product ratio[a]	**14** + **15** (% yield)[b]	de (%)[c]	de of **15** after crystallization[c] (%) (% yield)
1	H	benzene, reflux[d]	2	4:1	53	34	
2	H	DCM,[d] 20 °C	168	5.5:1		46	
3	H	DCM[e]		6:1	85	47	>99 (39)
4	H	DCM,[f] 20 °C	0.75	5.5:1		43	
5	H	DCM,[f] −18 °C	72	12:1	90	60	>99 (52)
6	*n*-Bu	benzene,[d] reflux	2	3.5:1	58	49	
7	*n*-Bu	DCM[e]		6:1	85	61	>99 (44)
8	*n*-Bu	DCM,[f] −18 °C	72	13:1	92	74	>99 (64)
9	Ph	DCM[e]		5:1	68	64	>99 (36)
10	Ph	DCM,[f] −18 °C	72	13:1	88	74	>99 (61)

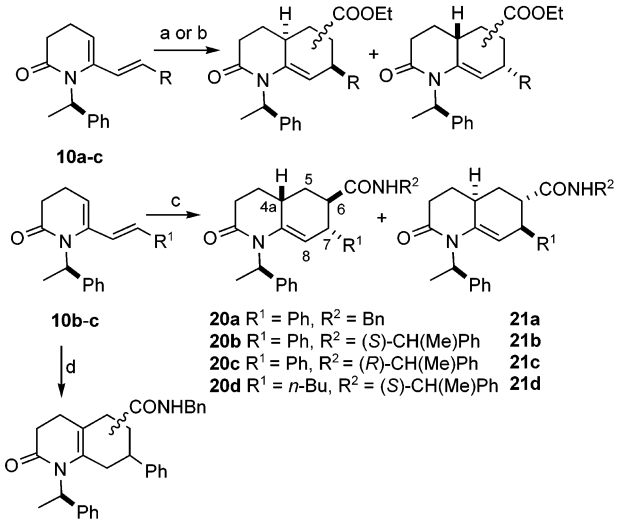
[a] By ^{1}H NMR of the crude reaction mixture. [b] After chromatography. [c] By ^{1}H NMR. [d] Concentration of diene 0.12 M, 1.5 equiv of *N*-phenylmaleimide. [e] A 0.08 M solution of diene was concentrated under vacuum by a rotary evaporator, heating with an external bath at 40 °C, 1.5 equiv of *N*-phenylmaleimide. [f] Concentration of diene 2.1 M, 1.5 equiv of *N*-phenylmaleimide.

With (S)-*N*-(1-phenylethyl)maleimide we observed the same endo/exo product ratio as above, but we incurred in a mismatched case, since the two endo products **14e** and **15e** were obtained in a 1:1 ratio.

The cycloaddition of dienes **13** (Scheme 3) with *N*-phenylmaleimide should in principle yield epimers of compounds **14** and **15**. However, phenyl-substituted diene **13a** did not react under any conditions, while *n*-butyl-substituted diene **13b** gave a low conversion to cycloadducts **18** and **19** (25% yield after chromatography, 72% de) after heating at 100 °C in toluene for 24 h. The steric clash between the distal *n*-butyl chain and the proton on C-5, which would destabilize the s-cis conformation, may be attributed to these results. The harsh reaction conditions caused also migration of the double bond. An NOE study on major isomer **19** allowed us to assign a cis relative stereochemistry of protons 4-H and 9b−H. This is consistent with an exo approach of the dienophile favored by the high reaction temperature. Moreover, pure compound **19** was obtained by $TiCl_4$-induced isomerization of **15b**. Thus its formation must have occurred by a prevailing attack of the dienophile on the "upper face" of the diene **13b** (the high de value of **19** excludes double bond isomerization followed by the cycloaddition reaction).

The cycloaddition of **10a−c** with *N*-phenylmaleimide provided, after crystallization, diastereo- and enantiopure, di- and trisubstituted octahydroquinolinones **15a−c** in good overall yield. The reactions occurred through a preferential endo approach of the dienophile, comparable to that previously reported for lactam-derived dienes.[1b,c,3h] The next step was to study the Diels−Alder reactions with monosubstituted dienophiles, such as acrylates and acrylamides, for which the prevailing regiochemical outcome had to be determined besides the facial and endo/exo selectivities. The reaction of **10a−c** with ethyl acrylate (Scheme 4) occurred by heating in toluene at 90 °C (24 h) or also at room temperature (4 d) when the concentration of the dienes was increased up to 2.8 M. In both cases, four major diastereomers (by ^{1}H NMR and HPLC analysis) were obtained but their separation was difficult and we could not assign the regiochemistry.[13] Two major diastereomers were instead obtained by

SCHEME 4[a]



[a] Key: (a) ethyl acrylate, toluene, 90 °C, 24 h; (b) CH_2Cl_2, rt, 4 days; (c) N-substituted acrylamide, CH_2Cl_2, rt or 50 °C; (d) *N*-benzylacrylamide, $TiCl_4$, CH_2Cl_2, 0−20 °C, 24 h.

reacting *N*-benzylacrylamide as the dienophile with **10c**: in this case, at a 2.8 M concentration of the diene (and 1.5 equiv of the acrylamide), the reaction proceeded, albeit slowly, at room temperature, to yield a roughly equimolar mixture of compounds **20a** and **21a** (not separated), in 46% yield after chromatography.[14] The low yield was attributed to the decomposition of starting material **10c** during the long reaction time (4 days). The regiochemistry of the two compounds, assigned by complete NMR analysis of the mixture, was in accordance with the theoretical predictions: apart from a weak coupling (3.3 Hz) with 8-H, in both **20a** and **21a** the proton on C-7 (which resonates at 3.72 and 3.49 ppm), couples with one proton only (i.e., with 6-H), thus excluding the 5-substituted regioisomer. The corresponding coupling constant (7.0 Hz) is indicative of an exo approach of the dienophile, since it is very close to that observed between the same protons in compound **20b**, whose trans relative stereochemistry was unambiguously assigned by X-ray analysis (see later).

Lewis acids could be used to enhance the regio- and stereoselectivity of these cycloadditions. With $AlCl_3$ and

(13) STO 3-21G* ab initio calculations allowed us to predict, for the reaction of dienes **10a−c** with ethyl acrylate, the formation of the 6-substituted products according to HOMO diene-LUMO dienophile interactions. In the case of **10b**, the exact ratio between the four major diastereomers was 2.3:2:1.2:1.

(14) Other unidentified cycloaddition products constituted less than 10% (by ^{1}H NMR) of the crude reaction mixture.

$TiCl_4$ at low temperature, complete decomposition of the dienes was observed when a preformed complex of the Lewis acid with ethyl acrylate was added to a cooled CH_2Cl_2 solution of **10a**−**c**, while with Et_2AlCl neither reaction nor decomposition occurred after 18 h at room temperature. It is possible that the Lewis acid exchanges with the amide group of **10** once the reagents are mixed, causing degradation of the dienes. Mixing 1 equiv of $AlCl_3$ and **10b** at −78 °C in CH_2Cl_2 affords a mixture of products deriving from ring opening, thus demonstrating that strong Lewis acids may cause the decomposition of these 2-(*N*-acylamino)-1,3-dienes.

Interestingly, the same process did not occur in the $TiCl_4$-catalyzed reaction of *N*-phenylmaleimide with **10a** (Scheme 2) or when a preformed complex of *N*-benzylacrylamide with $TiCl_4$ in CH_2Cl_2 was added to a solution of **10c** (Scheme 4). In the latter case, cycloaddition was complete after 24 h at 20 °C, yielding again only two diastereomers in a 2.3:1 ratio (regiochemistry not determined) with the usual isomerization of the double bond.

Because of the loss of a stereocenter in the Lewis acid-catalyzed reactions, we decided to avoid their use and exploit instead double-stereodifferentiated reactions with the aim of increasing the facial selectivity. This was done by preparing both enantiomers of the cheap, enantiopure *N*-(1-phenylethyl)acrylamide from acryloyl chloride and (*S*)- and (*R*)-1-phenylethylamine and reacting them with **10c** (Scheme 4). The expected reactions did not take place at room temperature and at high concentration (3 M) of the diene. The cycloadditions were complete after heating for 48 h at 50 °C a 2.8 M solution of **10c** in toluene in the presence of 1.5 equiv of the acrylamide. ^{1}H NMR analysis of the crude mixture revealed, in the case of the cycloaddition with (*S*)-*N*-(1-phenylethyl)acrylamide, the presence of two products in a 2:1 ratio. We were pleased to find out that the major product **20b** could easily be isolated by chromatography (28% yield; degradation of diene **10c** in the course of the reaction lowered the yield). As in the case of the reaction with *N*-benzylacrylamide, the cycloaddition with the chiral acrylamide *S* preferentially occurred according to anticipation on the basis of HOMO diene−LUMO dienophile interactions, affording the 6-substituted regioisomer. The trans stereochemical relationship of the two protons, arising from the exo approach, was assigned by X-ray analysis of **20b** (see the Supporting Information). This confirms the proclivity of diene **10c** to give exo cycloadducts with acrylamides. Again, the absolute stereochemistry of **20b** indicates that the dienophile preferentially approached the bottom face of the diene. The cycloaddition with the *R* acrylamide yielded instead two major products **20c** and **21c** in a ca. 1:1 ratio, one of which was obtained in pure form by chromatography. Analogously to the case above, NMR-based analysis[15] allowed us to assign the 6-regio- and relative trans stereochemistry of this diastereomer. We also carried out the cycloaddition of (*S*)-*N*-(1-phenylethyl)acrylamide with **10b**. The reaction takes place at 50 °C affording two major products in an approximately 2:1 ratio. The major diastereomer was isolated by chromatography (39%) and its structure determined by X-ray analysis.[11] Quite surprisingly, while the analysis confirmed the consistent 6-regiochemistry and relative trans stereochemistry of the two substituents, this major diastereomer resulted to be compound **21d** (see the Supporting Information) which derives from an "upper face" approach of the dienophile.[16]

The regioselectivity observed in the cycloadditions of imide-derived dienes **10** matches only in part what has been reported in the literature so far for the corresponding lactam-derived dienes. For example, the addition of ethyl acrylate in one case occurred according to theoretical predictions;[3e] however, in other cases an unexpected opposite regioselectivity has been observed.[3h] Interestingly, the same authors found that with chiral acrylamides as dienophiles, lactam-derived dienes gave predominantly the expected regioisomer (one exception only),[3h] thus in accordance with the results report herein.

Conclusions

In conclusion, we have for the first time carried out Stille, Suzuki−Miyaura, and Sonogashira cross-coupling reactions with an imide-derived vinyl phosphate to give in good to excellent yields enantiopure 2-(*N*-acylamino)-1,3-dienes that are potentially useful in Diels−Alder reactions for the construction of octahydroquinolinone rings. This has been demonstrated by reacting dienes **10a**−**c** with various dienophiles such as maleimides and acrylamides. One feature of dienes **10a**−**c** was their reactivity at low temperature, although with acrylamides a slight heating proved necessary to achieve cycloaddition. With maleimides, a preferential endo approach was observed and, regarding the facial selectivity, de values up to 74% were achieved. Diasteropure compounds were always obtained in good yield by crystallization. As for the regio preference, with acrylamides the reactions occurred according to theoretical predictions and showed proclivity toward the formation of the exo products. In the cycloadditions of (*R*)- and (*S*)-*N*-(1-phenylethyl)-acrylamide with **10b** and **10c**, the low facial diastereoselection (up to 33% de), compared to the reactions with *N*-phenylmaleimide, could be a consequence of a less congested transition state deriving from the exo approach of the dienophile. Despite this, the methodology maintains a synthetic usefulness, since the cycloaddition of chiral *N*-(1-phenylethyl)acrylamides consistently provides a major 6,7-disubstituted octahydroquinoline derivative which can be isolated in pure form by chromatography. Because of the number of available boronic acids (which are in any case easily prepared) and the possibility of controlling the absolute configuration of up to four stereocenters on the octahydroquinoline ring by changing the configuration of the chiral auxiliaries, the methodology is useful for a short synthesis of several, differently substituted octahydroquinoline derivatives in enantiopure form, further amenable to transformation into decahydroquinolines which could possess interesting biological activities.

(15) H-7 couples with only one proton on C-6 (which excludes the 5-regioisomer), with a $J = 6.8$ Hz very close to that between the same protons in **20b** (6.3 Hz).

(16) The reasons behind this stereochemical result have to be sought in the interaction between the two chiral residues and the *n*-butyl chain in the transition state of the process, although it is difficult at the present to suggest a model. It is interesting to observe that a similar "upper face" approach was prevailing in the formation of the exo product **19** in the reaction of *N*-phenylmaleimide with *n*-butyl substituted diene **13b**.

Experimental Section

All solvents were degassed before use. Chromatographic separations were performed under pressure on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. ^{1}H NMR, COSY, and NOESY spectra were recorded at 200 and 400 MHz; ^{13}C NMR spectra at 50.33 MHz. Molecular modeling was carried out by using the MM2* force field implemented in MacroModel v6.5 using the default values of the software for all calculations. Ab initio calculations were carried out through Spartan SGI 5.1.1, Wavefunction, Inc. using the default values of the software.

(*R*)-(+)-1-(1-Phenylethyl)piperidine-2,6-dione (6). To a solution of glutaric anhydride (9.730 g, 0.085 mol) in toluene (200 mL), kept under nitrogen atmosphere, was added dropwise a solution of (*R*)-(+)-1-phenylethylamine (11.0 mL, 0.085 mol) in toluene (40 mL). The solution was heated and allowed to reflux for 8 h. After the solution was cooled to room temperature, evaporation of the solvent gave an oil which was dissolved in $CHCl_3$ (350 mL). The organic solution was washed with 1 M HCl (2 × 100 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvent, the yellow oil was transferred into a flask equipped with a condenser and dissolved in acetyl chloride (30 mL). The solution was refluxed for 8 h, and then the excess of acetyl chloride was removed by distillation. The crude was dissolved in $CHCl_3$ (150 mL) and washed with saturated $NaHCO_3$(aq) (100 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the solid was chromatographed (CH_2Cl_2−MeOH, 40:1, R_f 0.65) to give pure **6** (4.14 g, 78%) as a white solid. As an alternative, pure **6** can be obtained by crystallization from EtOH: mp 123−124 °C (lit.[8] mp 124−127 °C); ^{1}H NMR ($CDCl_3$) δ 7.35−7.17 (m, 5 H), 6.04 (q, J = 7.3 Hz, 1 H), 2.62 (t, J = 6.6 Hz, 4 H), 1.90 (quintet, J = 6.6 Hz, 2 H), 1.74 (d, J = 7.3 Hz, 3 H).

(*R*)-Phosphoric Acid 6-Oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridin-2-yl Ester Diphenyl Ester (9). To a solution prepared by diluting with 6 mL of THF a 1 M solution of LHMDS in THF (3.31 mL, 3.31 mmol), cooled at 0 °C and under nitrogen atmosphere, was added dropwise and under stirring a solution of (*R*)-(+)-1-(1-phenylethyl)piperidine-2,6-dione **6** (0.720 g, 3.31 mmol) in THF (7 mL). The cooling bath was removed, and after 1 h at room temperature, the resulting suspension was cooled to −78 °C. A solution of diphenyl chlorophosphate (0.69 mL, 3.31 mmol) in THF (3 mL) was added, and after 10 min, the reaction mixture was allowed to warm to room temperature and left stirring for 1.5 h. After the addition of 10% NaOH (25 mL), the mixture was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried for 30 min over K_2CO_3. Evaporation of the solvent under vacuum yielded **9** (1.975 g) as an orange oil which was directly used for the next coupling steps: ^{1}H NMR ($CDCl_3$) δ 7.34−6.90 (m, 15 H), 5.89 (q, J = 7.0 Hz, 1 H), 5.28 (m, 1 H), 2.58−2.51 (m, 2 H), 2.30−2.20 (m, 2 H), 1.64 (d, J = 7.0 Hz, 3 H).

(*R*)-(−)-1-(1-Phenylethyl)-6-vinyl-3,4-dihydro-1*H*-pyridin-2-one (10a). Method A (Suzuki−Miyaura Coupling). MeONa (75 mg, 1.38 mmol) was added to a solution of vinylboronic acid dibutyl ester **11a** (0.30 mL, 1.38 mmol) in anhydrous THF (7 mL), cooled with an ice bath, under stirring and nitrogen atmosphere. The cooling bath was removed, and stirring was continued for 15 min. The resulting solution was added by syringe to a mixture of crude **9** (549 mg, ∼0.92 mmol) and $(Ph_3P)_4Pd$ (53 mg, 46 μmol) in THF (9 mL), and the reaction mixture was stirred for 2 h at 40 °C under a nitrogen atmosphere. Water (25 mL) was added and the reaction mixture extracted with Et_2O (3 × 20 mL). The combined organic layers were dried 30 min over K_2CO_3 and concentrated under vacuum to give a yellow-orange oil. Pure **10a** (139 mg, 66%) was obtained by chromatography (EtOAc−petroleum ether 1:5, 1% TEA, R_f 0.32) as a colorless oil.

Method B (Suzuki−Miyaura Coupling). To a stirred solution of crude **9** (632 mg, ∼1.06 mmol) in THF (14 mL), maintained under nitrogen atmosphere, were added 2 M Na_2CO_3 (aq) (7 mL), $(Ph_3P)_2PdCl_2$ (37 mg, 53 μmol), and **11a** (0.35 mL, 1.59 mmol). The mixture was stirred for 1.5 h at 40 °C, and then it was diluted with water (20 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over K_2CO_3 for 30 min and concentrated under vacuum to give an orange oil. Chromatography as above afforded pure **10a** (185 mg, 77%) as a colorless oil.

Method C (Stille Coupling). To a stirred solution of crude **9** (1.372 g, ∼2.30 mmol) in THF (12 mL) were added, under nitrogen atmosphere, tributyl(vinyl)tin (1.00 mL, 3.45 mmol), $(Ph_3P)_4Pd$ (106 mg, 92 μmol), and LiCl (975 mg, 23.0 mmol), and the mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with Et_2O (3 × 25 mL), and the organic phase was dried for 30 min over K_2CO_3. Evaporation of the solvent furnished an orange oil which was chromatographed as above to give pure **10a** (272 mg, 52%) as a colorless oil: $[\alpha]^{26}_D$ −30.6 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33−7.16 (m, 5 H), 5.92 (dd, J = 16.9, 10.6 Hz, 1 H), 5.70 (q, J = 7.3 Hz, 1 H), 5.46 (t, J = 5.0 Hz, 1 H), 5.35 (dd, J = 16.9, 1.5 Hz, 1 H), 4.89 (dd, J = 10.6, 1.5 Hz, 1 H), 2.58−2.47 (m, 2 H), 2.28−2.19 (m, 2 H), 1.70 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 142.1 (s), 141.7 (s), 132.6 (d), 128.2 (d, 2 C), 126.6 (d), 126.2 (d, 2 C), 116.2 (t), 108.2 (d), 51.6 (d), 32.7 (t), 19.3 (t), 17.7 (q); MS *m*/*z* 227 (M^+, 14), 105 (100). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.98; H, 7.54; N, 6.50.

(*R*)-(−)-6-[(*E*)-Hex-1-enyl]-1-(1-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one (10b). To a stirred solution of crude **9** (1.492 g, ∼2.50 mmol) in THF (30 mL) were added, under nitrogen atmosphere, 2 M Na_2CO_3 (aq) (15 mL), $(Ph_3P)_2PdCl_2$ (88 mg, 125 μmol), and hex-1-enylboronic acid **11b** (480 mg, 3.75 mmol). The mixture was heated to 40 °C, left under stirring 1 h, and after cooling, diluted with water (30 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was dried for 30 min over K_2CO_3 and concentrated in vacuo. The crude brown oil was chromatographed (EtOAc−petroleum ether 1:4, 1% TEA, R_f 0.39) to give **10b** (582 mg, 82%) as a yellowish oil: $[\alpha]^{24}_D$ −22.4 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.17 (m, 5 H), 5.84−5.66 (m, 2 H), 5.52 (d, J = 15.4 Hz, 1 H), 5.32 (t, J = 5.0 Hz, 1 H), 2.54−2.46 (m, 2 H), 2.26−2.16 (m, 2 H), 1.91−1.82 (m, 2 H), 1.70 (d, J = 7.3 Hz, 3 H), 1.22−1.14 (m, 4 H), 0.87−0.80 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 142.3 (s), 141.5 (s), 133.6 (d), 128.1 (d, 2 C), 126.4 (d), 126.2 (d, 2 C), 125.3 (d), 106.9 (d), 51.4 (d), 32.8 (t), 32.0 (t), 30.9 (t), 22.1 (t), 19.3 (t), 17.6 (q), 13.8 (q); MS *m*/*z* 283 (M^+, 8), 103 (100). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.36; H, 8.66; N, 4.83.

(*R*)-(−)-1-(1-Phenylethyl)-6-[(*E*)-styryl]-3,4-dihydro-1*H*-pyridin-2-one (10c). To a stirred solution of crude **9** (794 mg, ∼1.33 mmol) in THF (18 mL), were added, under nitrogen atmosphere, 2 M Na_2CO_3 (aq) (9 mL), $(Ph_3P)_2PdCl_2$ (47 mg, 67 μmol), and *trans*-2-phenylvinylboronic acid **11c** (296 mg, 2.00 mmol). The mixture was stirred for 3 h at 40 °C, diluted with water (20 mL), and extracted with Et_2O (3 × 20 mL). The organic phase was dried for 30 min over K_2CO_3 and concentrated in vacuo. Chromatography of the crude (EtOAc−petroleum ether 1:5, 1% TEA, R_f 0.33) gave **10c** (343 mg, 85%) as a yellowish oil: $[\alpha]^{22}_D$ −104.9 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31−7.16 (m, 8 H), 7.10−7.06 (m, 2 H), 6.61 (d, J = 15.8 Hz, 1 H), 6.16 (d, J = 15.8 Hz, 1 H), 5.94 (q, J = 7.0 Hz, 1 H), 5.57 (t, J = 5.5 Hz, 1 H), 2.61−2.53 (m, 2 H), 2.33−2.28 (m, 2 H), 1.69 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.4 (s), 142.2 (s), 141.0 (s), 136.2 (s), 130.2 (d), 128.4 (d, 2 C), 128.2 (d, 2 C), 127.2 (d), 126.6 (d), 126.3 (d), 126.2 (d), 123.7 (d), 108.3 (d), 50.9 (d), 32.5 (t), 19.3 (t), 17.6 (q); MS *m*/*z* 303 (M^+, 20), 104 (100). Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.29; H, 6.62; N, 4.79.

(*R*)-(−)-6-[(*Z*)-(1-Ethylbut-1-enyl)-1-(1-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one (10d). To a stirred solution of crude **9** (883 mg, ∼1.48 mmol) in THF (20 mL) were added, under nitrogen atmosphere, 2 M Na_2CO_3 (aq) (10 mL), $(Ph_3P)_2PdCl_2$ (52 mg, 74 μmol), and 2-[(*Z*)-1-ethylbut-1-enyl]benzo-1,3,2-dioxaborole **11d** (448 mg, 2.22 mmol). The mixture was stirred 1 h at 40 °C, diluted with water (30 mL), and extracted with Et_2O (3 × 40 mL). The organic phase was dried for 30 min over K_2CO_3 and concentrated in vacuo. Chromatography (EtOAc − petroleum ether 1:5, 1% TEA, R_f 0.47) yielded **10d** (292 mg, 70%) as a colorless oil: $[\alpha]^{25}_D$ −101.1 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33−7.13 (m, 5 H), 5.51 (t, *J* = 7.3 Hz, 1 H), 5.19 (t, *J* = 4.8 Hz, 1 H), 4.86 (q, *J* = 7.0 Hz, 1 H), 2.55−2.25 (m, 2 H), 2.22−1.87 (m, 6 H), 1.82 (d, *J* = 7.0 Hz, 3 H), 0.97 (t, *J* = 7.7 Hz, 3 H), 0.96 (t, *J* = 7.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.4 (s), 145.8 (s), 142.4 (s), 138.2 (s), 133.1 (d), 127.9 (d, 2 C), 126.3 (d, 2 C), 108.8 (d), 54.5 (d), 33.4 (t), 21.9 (t), 20.9 (t), 19.3 (t), 17.6 (q), 13.9 (q), 12.8 (q); MS *m*/*z* 283 (M^+, 14), 105 (100). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.19; H, 8.97; N, 4.58.

(*R*)-(+)-1-(1-Phenylethyl)-6-phenylethynyl-3,4-dihydro-1*H*-pyridin-2-one (12a). To a solution of crude **9** (1.295 g, ∼2.17 mmol) in TEA (11 mL) and $CHCl_3$ (3.5 mL) were added under nitrogen atmosphere phenylacetylene (0.24 mL, 2.17 mmol), CuI (41 mg, 0.22 mmol), and $(Ph_3P)_2PdCl_2$ (76 mg, 0.11 mmol), and the mixture was stirred for 1 h at 50 °C. Then water (20 mL) was added and the mixture extracted with Et_2O (5 × 20 mL). The combined organic layers were dried for 30 min over K_2CO_3 and concentrated. Chromatography of the brown-black oil (EtOAc−petroleum ether 1:4, 1% TEA, R_f 0.39) provided **12a** (571 mg, 87%) as an orange oil: $[\alpha]^{22}_D$ +14.1 (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34−7.19 (m, 8 H), 7.18−7.10 (m, 2 H), 6.05 (q, *J* = 7.3 Hz, 1 H), 5.82 (t, *J* = 5.1 Hz, 1 H), 2.63−2.55 (m, 2 H), 2.42−2.33 (m, 2 H), 1.84 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8 (s), 141.6 (s), 131.2 (d, 2 C), 128.5 (d), 128.1 (d, 2 C), 128.0 (d, 2 C), 126.4 (d, 2 C), 124.3 (s), 122.0 (s), 118.1 (d), 91.2 (s), 83.9 (s), 51.3 (d), 31.8 (t), 20.3 (t), 17.2 (q); MS *m*/*z* 301 (M^+, 6), 102 (100). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 84.87; H, 5.96; N, 4.50.

(*R*)-(+)-6-Hex-1-ynyl-1-(1-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one (12b). To a solution of crude **9** (871 mg, ∼1.46 mmol) in TEA (8 mL) and $CHCl_3$ (2.5 mL) were added, under nitrogen atmosphere, 1-hexyne (0.17 mL, 1.46 mmol), CuI (28 mg, 0.15 mmol), and $(Ph_3P)_2PdCl_2$ (51 mg, 73 μmol), and the mixture was stirred for 1 h at 50 °C. Water (15 mL) was added and the mixture extracted with Et_2O (5 × 15 mL). The organic phase was dried over K_2CO_3 and concentrated in vacuo. The brown-black crude oil was chromatographed (EtOAc−petroleum ether 1:5, 1% TEA, R_f 0.30) to yield **12b** (261 mg, 64%) as a yellowish oil: $[\alpha]^{22}_D$ +86.0 (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33−7.15 (m, 5 H), 5.90 (q, *J* = 7.1 Hz, 1 H), 5.60 (t, *J* = 4.8 Hz, 1 H), 2.58−2.37 (m, 2 H), 2.32−2.22 (m, 2 H), 2.13−2.06 (m, 2 H), 1.79 (d, *J* = 7.1 Hz, 3 H), 1.56−1.19 (m, 4 H), 0.96−0.80 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.9 (s), 141.8 (s), 127.9 (d, 2 C), 126.4 (d, 2 C), 126.3 (d), 124.9 (s), 116.0 (d), 92.9 (s), 75.2 (s), 51.8 (d), 32.0 (t), 30.0 (t), 21.9 (t), 20.1 (t), 18.8 (t), 17.0 (q), 13.5 (q); MS *m*/*z* 281 (M^+, 5), 102 (100). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.98; H, 8.54; N, 4.57.

(+)-(3a*R*,9a*R*,9b*S*)-2-Phenyl-6-[(*R*)-1-phenyl-ethyl]-4,6,8,9,9a,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinoline-1,3,7-trione (15a). Method A. A solution of **10a** (90 mg, 0.40 mmol) and *N*-phenylmaleimide (103 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) was concentrated under vacuum by a rotary evaporator, heating with an external bath at 40 °C. The crude mixture obtained just after complete evaporation of the solvent was chromatographed (EtOAc−petroleum ether, 1:1) to give a mixture of exo products (R_f 0.38, 19 mg, 12%) and the mixture of endo products **14a** and **15a** (R_f 0.15, 135 mg, 85%). Pure **15a** (62 mg, 39%, colorless crystals) was obtained by crystallization from cyclohexane/EtOAc as follows: the diastereomeric mixture was suspended in cyclohexane (4.5 mL) and heated to reflux. The minimum amount of EtOAc was added dropwise to completely dissolve the products and then the solution was slowly cooled to room temperature. After 24 h, the solvent was removed and the crystals were washed with cyclohexane (2 × 0.5 mL).

Method B. *N*-Phenylmaleimide (29 mg, 0.16 mmoli) was added to a solution of **10a** (25 mg, 0.11 mmol) in CH_2Cl_2 (52 μL) cooled at −18 °C, and the resulting mixture was stirred for 3 days. After evaporation of the solvent, chromatography (EtOAc−petroleum ether, 1:1) gave the mixture of exo products (R_f 0.38, 3 mg, 7%) and the mixture of endo products **14a** and **15a** (R_f 0.15, 40 mg, 90%). Crystallization as above gave pure **15a** (23 mg) in 52% yield: mp 198−199 °C; $[\alpha]^{25}_D$ +7.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.40 (m, 3 H), 7.16−7.08 (m, 7 H), 5.75 (q, *J* = 7.0 Hz, 1H), 5.07 (dt, *J* = 7.8, 2.7 Hz, 1 H), 3.32 (dd, *J* = 9.0, 5.5 Hz, 1 H), 3.24 (ddd, *J* = 9.0, 7.4, 1.2 Hz, 1 H), 2.92−2.75 (m, 4 H), 2.44−2.35 (m, 1 H), 2.25 (ddd, *J* = 7.4, 3.5, 2.0 Hz, 1 H), 2.17−2.10 (m, 1 H), 1.74 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.1 (s), 176.3 (s), 170.3 (s), 140.3 (s), 138.6 (s), 131.5 (s), 128.9 (d, 2 C), 128.5 (d, 2 C), 126.6 (d), 126.3 (d, 2 C), 125.8 (d, 2 C), 103.7 (d), 53.1 (d), 43.8 (d), 40.3 (d), 35.6 (d), 33.3 (t), 24.3 (t), 20.8 (t), 16.6 (q); MS *m*/*z* 400 (M^+, 7), 105 (100). Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H 6.04; N 7.00. Found: C, 75.52; H 6.02; N 7.10.

(+)-(3a*R*,4*R*,9a*R*,9b*S*)-4-Butyl-2-phenyl-6-[(*R*)-1-phenylethyl]-4,6,8,9,9a,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinoline-1,3,7-trione (15b). Method A. A solution of **10b** (82 mg, 0.29 mmol) and *N*-phenylmaleimide (75 mg, 0.43 mmol) in CH_2Cl_2 (3.5 mL) was concentrated under vacuum as described above. Chromatography (EtOAc−petroleum ether, 2:3) gave a mixture of exo products (R_f 0.38, 19 mg, 14%) and the mixture of endo products **14b** and **15b** (R_f 0.17, 113 mg, 85%). Crystallization from cyclohexane/EtOAc provided pure **15b** (58 mg, 44%, colorless crystals).

Method B. *N*-Phenylmaleimide (28 mg, 0.16 mmol) was added to a solution of **10b** (31 mg, 0.11 mmol) in CH_2Cl_2 (52 μL) cooled at −18 °C, and the mixture was stirred for 3 days. After evaporation of the solvent, chromatography gave a mixture of exo products (3 mg, 5%) and the mixture of endo products **14b** and **15b** (45 mg, 92%). Crystallization as above yielded pure **15b** (32 mg, colorless crystals) in 64% yield: mp 162−164 °C; $[\alpha]^{25}_D$ +40.7 (*c* 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.38 (m, 3 H), 7.19−7.08 (m, 7 H), 5.63 (q, *J* = 7.0 Hz, 1H), 4.94 (t, *J* = 2.7 Hz, 1 H), 3.31 (dd, *J* = 8.6, 5.1 Hz, 1 H), 3.23 (dd, *J* = 8.6, 6.7 Hz, 1 H), 2.93−2.71 (m, 3 H), 2.42−2.27 (m, 2 H), 2.17−2.10 (m, 1 H), 1.94−1.85 (m, 1 H), 1.75 (d, *J* = 7.0 Hz, 3 H), 1.62−1.54 (m, 1 H), 1.51−1.43 (m, 1 H), 1.40−1.32 (m, 3 H), 0.93 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.0 (s), 175.5 (s), 170.2 (s), 140.4 (s), 138.4 (s), 131.6 (s), 128.8 (d, 2 C), 128.4 (d, 2 C), 126.6 (d), 126.3 (d, 2 C), 125.9 (d, 2 C), 109.5 (d), 53.6 (d), 44.6 (d), 43.9 (d), 36.8 (d), 36.0 (d), 33.3 (t), 31.2 (t), 30.4 (t), 22.5 (t), 20.7 (t) 16.7 (q), 14.0 (q); MS *m*/*z* 351 (M^+ − 105, 47), 103 (100). Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H 7.06; N 6.14. Found: C, 76.68; H 7.06; N 6.28.

(+)-(3a*R*,4*R*,9a*R*,9b*S*)-2,4-Diphenyl-6-[(*R*)-1-phenylethyl]-4,6,8,9,9a,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinoline-1,3,7-trione (15c). Method A. A solution of **10c** (268 mg, 0.88 mmol) and *N*-phenylmaleimide (229 mg, 1.32 mmol) in CH_2Cl_2 (10 mL) was concentrated under vacuum as described above. Chromatography (EtOAc−petroleum ether, 3:2) gave a mixture of exo products (R_f 0.60, 88 mg, 21%) and the mixture of endo products **14c** and **15c** (R_f 0.23, 284 mg, 68%). Crystallization as above furnished pure **15c** (152 mg, 36%, colorless crystals).

Method B. *N*-Phenylmaleimide (33 mg, 0.19 mmol) was added to a solution of **10c** (39 mg, 0.13 mmol) in CH_2Cl_2 (61 μL) cooled at −18 °C, and the mixture was allowed to stir for 3 days. Chromatography gave the exo product mixture (4 mg, 7%) and the mixture of endo products **14c** and **15c** (54 mg,

88%). Crystallization as above furnished pure **15c** (37 mg) in 61% yield: mp 216−218 °C; $[\alpha]^{25}_D$ +108.5 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.35 (m, 3 H), 7.33−7.26 (m, 3 H), 7.21−7.19 (m, 2 H), 7.13−7.03 (m, 5 H), 6.84−6.81 (m, 2 H), 6.12 (q, J = 7.0 Hz, 1 H), 5.20−5.19 (m, 1 H), 3.73−3.70 (m, 1 H), 3.40−3.34 (m, 2 H), 3.17−3.07 (m, 1 H), 2.91−2.85 (m, 2 H), 2.50−2.42 (m, 1 H), 2.21−2.14 (m, 1 H), 1.71 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.5 (s), 174.1 (s), 170.4 (s), 149.9 (s), 139.7 (s), 137.2 (s), 131.5 (s), 128.6 (d, 4 C), 128.5 (d, 2 C), 128.3 (d, 2 C), 128.2 (d), 127.2 (d), 126.7 (d), 126.4 (d, 2 C), 126.1 (d, 2 C), 108.4 (d), 51.6 (d), 47.1 (d), 44.7 (d), 42.0 (d), 35.6 (d), 33.3 (t), 21.0 (t), 15.5 (q); MS *m*/*z* 476 (M^+, 9), 104 (100). Anal. Calcd for $C_{31}H_{28}N_2O_3$: C, 78.13; H 5.92; N 5.88. Found: C, 78.03; H 5.91; N 6.07.

(3a*R*,9b*R*)-2-Phenyl-6-[(*R*)-1-phenylethyl]-4,5,6,8,9,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinolin-1,3,7-trione (17a). To a solution of **15a** (9 mg, 0.022 mmol) in anhydrous CH_2Cl_2 (5 mL), cooled at −78 °C and under nitrogen atmosphere, was slowly added a solution of 1 M $TiCl_4$ in CH_2Cl_2 (0.03 mL, 0.03 mmol). After 15 min of stirring, 1 mL of water was added and the mixture allowed to warm to room temperature. When the ice completely melted, another 5 mL of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and dried over Na_2SO_4. After evaporation of the solvent, **17a** (9 mg) was obtained (95% conversion by ^{1}H NMR): ^{1}H NMR ($CDCl_3$) δ 7.47−7.36 (m, 3 H), 7.30−7.09 (m, 7 H), 6.00 (q, J = 7.3 Hz, 1 H), 3.59 (d, J = 8.4 Hz, 1 H), 3.26−3.12 (m, 1 H), 2.88−2.66 (m, 1 H), 2.61−2.54 (m, 2 H), 2.41−2.27 (m, 1 H), 2.10−2.02 (m, 2 H), 1.69 (d, J = 7.3 Hz, 3 H), 1.62−1.19 (m, 2 H).

(3a*R*,4*R*,9b*R*)-4-Butyl-2-phenyl-6-[(*R*)-1-phenylethyl]-4,5,6,8,9,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinolin-1,3,7-trione (19). To a solution of **15b** (3 mg, 0.007 mmol) in anhydrous CH_2Cl_2 (0.25 mL), cooled at −78 °C and under nitrogen atmosphere, was slowly added a solution of 1 M $TiCl_4$ in CH_2Cl_2 (0.01 mL, 0.01 mmol). Workup as reported above for **17a** furnished **19** (3 mg, 100%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.48−7.36 (m, 3 H), 7.29−7.10 (m, 7 H), 5.97 (q, J = 7.0 Hz, 1H), 3.59 (d, J = 8.1 Hz, 1 H), 3.18 (dd, J = 8.1, 4.4 Hz, 1 H), 2.76−2.64 (m, 1 H), 2.60−2.53 (m, 2 H), 2.38−2.28 (m, 1 H), 2.17−2.10 (m, 1 H), 1.93−1.83 (m, 1 H), 1.78−1.09 (m, 7 H), 1.71 (d, J = 7.0 Hz, 3 H), 0.90−0.73 (m, 3 H).

Preparation of *N*-Benzylacrylamide. Acryloyl chloride (0.50 mL, 6.20 mmol) and then, dropwise, a solution of benzylamine (0.74 mL, 6.82 mmol) in TEA (1.03 mL, 7.44 mmol) were added to cold (0−5 °C) CH_2Cl_2 (10 mL) under nitrogen atmosphere. The resulting white suspension was allowed to stir for 16 h at room temperature, diluted with CH_2Cl_2 (5 mL), washed with water (10 mL), 1 M H_2SO_4 (10 mL), 1 M $NaHCO_3$ (10 mL), and brine (10 mL), and finally dried over Na_2SO_4. After evaporation of the solvent, the acrylamide was obtained as a white solid (989 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.21 (m, 5 H), 6.30 (dd, J = 17.2, 1.8 Hz, 1 H), 6.08 (dd, J = 17.2, 9.9 Hz, 1 H), 5.95 (br s, 1 H), 5.63 (dd, J = 9.9, 1.8 Hz, 1 H), 4.48 (d, J = 5.5 Hz, 2 H).

(*S*)-*N*-(1-Phenylethyl)acrylamide. Prepared as reported above for *N*-benzylacrylamide. Starting from acryloyl chloride (1.62 mL, 20 mmol) and (*S*)-(−)-1-phenylethylamine (2.84 mL, 22 mmol), the pure title compound (3.403 g, 97%) was obtained after chromatography (EtOAc−petroleum ether, 2:3, R_f 0.31) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.32−7.23 (m, 5 H), 6.27 (dd, J = 16.8, 1.5 Hz, 1 H), 6.05 (dd, J = 16.8, 10.3 Hz, 1 H), 5.79 (br-s, 1 H), 5.61 (dd, J = 10.3, 1.5 Hz, 1 H), 5.19 (quintet, J = 7.0 Hz, 1 H), 1.50 (d, J = 7.0 Hz, 3 H).

(*R*)-*N*-(1-Phenylethyl)acrylamide. Prepared as reported above for *N*-benzylacrylamide, starting from acryloyl chloride (1.62 mL, 20 mmol) and (*R*)-(−)-1-phenylethylamine (2.84 mL, 22 mmol), the pure title compound (3.302 g, 95%) was obtained as a white solid after chromatography.

(−)-(4a*R*,6*R*,7*R*)-2-Oxo-7-phenyl-1-(*R*)-(1-phenylethyl)-1,2,3,4,4a,5,6,7-octahydroquinoline-6-carboxylic Acid (*S*)-(1-Phenylethyl)amide (20b). To a solution of **10c** (349 mg, 1.15 mmol) in toluene (0.41 mL) was added (*S*)-*N*-(1-phenylethyl)acrylamide (302 mg, 1.73 mmol), and the mixture was allowed to react under stirring for 48 h at 50 °C, with monitoring by TLC. After evaporation of the solvent, the crude was chromatographed (EtOAc−petroleum ether 3:2, R_f 0.33) to give **20b** (152 mg, 28%) as a colorless solid. Colorless crystals for X-ray analysis were obtained from ethyl acetate−cyclohexane as reported above: mp 184−185 °C; $[\alpha]^{23}_D$ −68.3 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.12 (m, 13 H), 6.88−6.81 (m, 2 H), 6.28 (q, J = 7.3 Hz, 1 H), 5.29 (d, J = 7.3 Hz, 1 H), 4.99 (quintet, J = 7.3 Hz, 1 H), 4.95−4.90 (m, 1 H), 3.70−3.67 (m, 1 H), 2.88−2.55 (m, 2 H), 2.45−2.34 (m, 1 H), 2.30−2.04 (m, 2 H), 1.90−1.59 (m, 3 H), 1.66 (d, J = 7.3 Hz, 3 H), 1.19 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.6 (s), 169.3 (s), 143.6 (s), 143.0 (s), 141.6 (s), 137.1 (s), 128.5 (d), 128.3 (d), 128.2 (d), 127.6 (d), 127.2 (d), 126.5 (d), 126.3 (d), 126.0 (d), 125.5 (d), 111.7 (d), 50.4 (d), 48.4 (d), 47.2 (d), 43.2 (d), 32.8 (d), 32.7 (t), 30.3 (t), 27.0 (t), 21.3 (q), 15.3 (q); MS *m*/*z* 478 (M^+, 25), 105 (100). Anal. Calcd for $C_{32}H_{34}N_2O_2$: C, 80.30; H 7.16; N 5.85. Found: C, 80.54; H 7.17; N 5.79.

(−)-(4a*S*,6*S*,7*S*)-7-Butyl-2-oxo-1-(*R*)-(1-phenylethyl)-1,2,3,4,4a,5,6,7-octahydroquinoline-6-carboxylic Acid (*S*)-(1-Phenylethyl)amide (21d). To a solution of **10b** (371 mg, 1.31 mmol) in toluene (0.47 mL) was added (S)-*N*-(1-phenylethyl)acrylamide (344 mg, 1.97 mmol), and the mixture was allowed to react under stirring for 3 days at 50 °C. After evaporation of the solvent and chromatography (EtOAc−petroleum ether, 3:2), the major diastereomer **21d** (R_f 0.17, 234 mg, 39%) was obtained as a white solid. Colorless crystals were obtained from *n*-hexane/EtOAc: mp 136−137 °C; $[\alpha]^{25}_D$ +82.8 (*c* 0.24, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.14 (m, 10 H), 6.04 (q, J = 7.3 Hz, 1H), 5.66 (d, J = 7.3 Hz, 1H), 5.11 (quintet, J = 7.3 Hz, 1 H), 4.93 (br s, 1 H), 2.68−2.36 (m, 2 H), 2.15−1.96 (m, 4 H), 1.78−1.44 (m, 3 H), 1.72 (d, J = 7.3 Hz, 3 H), 1.38 (d, J = 7.3 Hz, 3 H), 1.29−1.10 (m, 6 H), 0.90−0.80 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.7 (s), 169.5 (s), 143.3 (s), 140.8 (s), 137.0 (s), 128.4 (d, 2 C), 128.2 (d, 2 C), 127.2 (d), 126.4 (d), 126.0 (d, 2 C), 110.9 (d), 52.1 (d), 48.2 (d), 43.6 (d), 36.1 (d), 35.0 (t), 33.0 (t), 32.8 (d), 30.7 (t), 29.0 (t), 26.8 (t), 22.6 (t), 21.4 (q), 17.2 (q), 13.9 (q); MS *m*/*z* 458 (M^+,-10), 103 (100). Anal. Calcd for $C_{30}H_{38}N_2O_2$: C, 78.56; H 8.35; N 6.11. Found: C, 78.44; H 8.36; N 6.07.

X-ray Crystallographic Determination of Compounds 15a−c, 20b, and 21d. Compound **15a**: $C_{25}H_{24}N_2O_3$, M = 400.46, orthorhombic, space group $P2_12_12_1$ a = 8.524(1) Å, b = 10.040(3) Å, c = 24.132(5) Å, V = 2065.2(8) Å^3, Z = 4, F(000) = 848, μ = 0.682 mm^{-1}, D_c = 1.288 g/cm^{-3}. The reflections collected were 2530, of which 2343 unique ($2\theta_{max}$ = 130°). In determining and refining the structure, 2222 reflections and 277 parameters were used; the final agreement factor was R = 0.0472 for reflections having $I > 2\sigma(I)$ and 0.0489 for all data.

Compound **15b**: $C_{29}H_{32}N_2O_3$, M = 456.57, orthorhombic, space group $P2_12_12_1$, a = 9.079(1) Å, b = 9.920(1) Å, c = 27.771-(2) Å, V = 2501.2(4) Å^3, Z = 4, F(000) = 976, μ = 0.621 mm^{-1}, D_c = 1.212 g/cm^{-3}. The reflections collected were 2632, of which 2443 unique ($2\theta_{max}$ = 120°). In determining and refining the structure, 2117 reflections and 317 parameters were used; the final agreement factor was R = 0.0673 for reflections having $I > 2\sigma(I)$ and 0.0737 for all data.

Compound **15c**: $C_{31}H_{28}N_2O_3$, M = 476.55, monoclinic, space group $P2_1$, a = 8.986(1) Å, b = 9.522(1) Å, c = 14.420(1) Å, β = 90.139(2)°, V = 1233.8(2) Å^3, Z = 2, F(000) = 504, μ = 0.659 mm^{-1}, D_c = 1.283 g/cm^3. The reflections collected were 3684, of which 2239 unique ($2\theta_{max}$ = 108°). In determining and refining the structure, 1791 reflections and 331 parameters were used; the final agreement factor was R = 0.0460 for reflections having $I > 2\sigma(I)$ and 0.0638 for all data.

Compound **20b**: $C_{32}H_{34}N_2O_2$, M = 478.61, monoclinic, space group $P2_1$, a = 10.191(1) Å, b = 13.857(2) Å, c = 10.568(1) Å, β = 114.60(2)°, V = 1356.9(3) Å^3, Z = 2, F(000) = 512, μ = 0.568 mm^{-1}, D_c = 1.171 g/cm^3. The reflections collected were 2686, of which 2289 unique ($2\theta_{max}$ = 120°). In determining and

refining the structure, 2153 reflections and 355 parameters were used; the final agreement factor was $R = 0.055$ for reflections having $I > 2\sigma(I)$ and 0.057 for all data.

Compound **21d**: $C_{30}H_{38}N_2O_2$, $M = 458.62$, orthorhombic, space group $P2_12_12_1$, $a = 9.415(1)$ Å, $b = 9.884(1)$ Å, $c = 30.493(2)$ Å, $V = 2837.6(5)$ Å^3, $Z = 4$, $F(000) = 992$, $\mu = 0.518$ mm^{-1}, $D_c = 1.074$ g/cm^3. The reflections collected were 6277, of which 2931 unique ($2\theta_{max} = 112°$). In determining and refining the structure, 2931 reflections and 309 parameters were used; the final agreement factor was $R = 0.0915$for reflections having $I > 2\sigma(I)$ and 0.1498 for all data.

Data sets for **15a**, **15b**, and **20b** were collected on a Bruker P4 X-ray diffractometer using the (Cu Kα) radiation ($\lambda = 1.5418$ Å) for the cell parameter determinations and data collections. The intensities of two standard reflections were monitored during data collections to check the stability of the crystals; no loss of intensity was recognized. In case of **15c** and **21d**, the analysis was carried out with a Bruker CCD X-ray diffractometer and Crossed Gobel mirrors monochromated Cu Kα radiation was used for cell parameter determination and data collection. The intensities of some equivalents were monitored during data collection to check the stability of the crystal. The data acquisition, integration, and data reduction were performed using SMART and SAINT programs.[17] In all cases, the integrated intensities, measured at room temperature (293 K), were corrected for Lorentz and polarization effects.[18] Hydrogen atom positions were calculated (C−H = 0.96 Å), except for H_6 in **15a,** H_6 in **15b**, H_3, H_4, H_5, H_6, H_8 in **15c**, and H_N, H_1, H_3, H_8, H_9, H_{17} and H_{25} in **20b** which were found in the Fourier difference synthesis; all of them were refined as isotropic. Anisotropic thermal parameters were used for all the non hydrogen atoms. The structures were solved by direct methods of SIR97[19] and refined using the full-matrix least squares on F2 provided by SHELXL97.[20]

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Supporting Information Available: ORTEP plots for **15a**−**c**, **20b**, and **21d**. X-ray crystallographic information files for **15a**−**c**, **20b**, and **21d.** ^{1}H NMR spectra of **15a**−**c**, **20b**, and **21d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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