JOC Notes

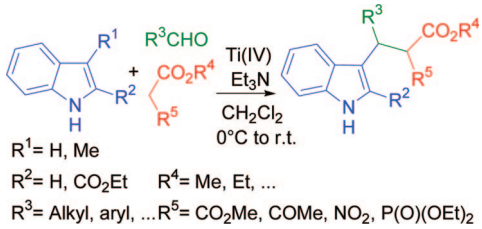
$TiCl_4/Et_3N$-Promoted Three-Component Condensation between Aromatic Heterocycles, Aldehydes, and Active Methylene Compounds

Andrea Renzetti,[†,‡] Emmanuel Dardennes,[†] Antonella Fontana,[‡] Paolo De Maria,[‡] Janos Sapi,*[,†] and Stéphane Gérard*[,†]

Institut de Chimie Moléculaire de Reims, UMR CNRS 6229, Université de Reims-Champagne-Ardenne, Faculté de Pharmacie, 51 rue Cognacq-Jay, F-51096 Reims, Cedex, France, and Dipartimento di Scienze del Farmaco, Università "G. d'Annunzio", via dei Vestini 31, I-66013 Chieti, Italy

janos.sapi@univ-reims.fr; stephane.gerard@univ-reims.fr

Received March 7, 2008



A one-pot methodology for the synthesis of polyfunctionalized indole derivatives by a $TiCl_4/Et_3N$-promoted trimolecular condensation of aldehydes, indole heterocycles, and various activated carbonyl compounds is reported. Rationalization of these reactions and extension to other heterocyclic systems is also described.

Since the publication of the Strecker reaction in 1850, which could be considered as the beginning of the multicomponent reaction (MCR) story,[1] this strategy has been shown to be a valuable tool in the preparation of structurally diverse chemical libraries of druglike heterocyclic compounds.[2] MCRs often involve domino processes with at least three different simple partners reacting in a well-defined manner to create complexity and diversity by the facile formation of several new bonds. This methodology is particularly well adapted for combinatorial chemistry. The usefulness of MCRs is even greater if they provide access to "privileged medicinal scaffolds" like, for example, pyridines and 1,4-dihydropyridines, decahydroquinolin-4-ones, or dihydropyrimidines.[3–5]

In previous works, we have shown that the Yonemitsu trimolecular condensation,[6] involving indole, Meldrum's acid, and an aldehyde combined with simple functional group transformations, was efficient for the synthesis of various β-substituted tryptophans, heterocycle-fused tryptamines, β-carbolines, and carbazoles of biological interest.[7]

Toward a direct approach of such tryptophans and heterocyclic systems, we have envisaged the replacement of the Meldrum's acid moiety by malonesters and other 1,3-bifunctional carbonyl derivatives like acetoacetates, nitroacetates, and phosphonoacetates. As the above-mentioned active methylene compounds failed to react under the usual Yonemitsu reaction conditions[6] probably due to their higher pK_a values, we focused our attention to a Lewis acid activated version. Lewis acids have been well documented to facilitate numerous C−C bond formation reactions. In particular, in the 1970's, Lehnert[8] and later on Reetz[9] described various Ti(IV) derivative-promoted syntheses of Knoevenagel adducts. Although Ti(IV)-catalyzed Knoevenagel reactions have scarcely been documented[10] since that time, we chose this approach to extend our trimolecular condensation to various activated carbonyl compounds.

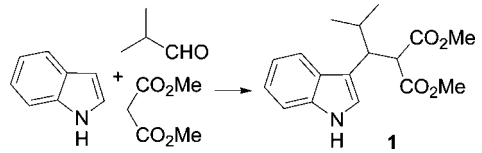
We speculated that titanium species would not only help the formation of the corresponding enolate but could also promote Friedel−Crafts-type reaction between indole and an in situ formed Knoevenagel intermediate. Friedel−Crafts alkylation of indoles with α,β-unsaturated carbonyl derivatives,[11] especially the Lewis acid catalyzed asymmetric version,[12] have recently attracted great attention, but its multicomponent version remains unprecedented.

[†] Université de Reims-Champagne-Ardenne.
[‡] Università "G. d'Annunzio".

(1) Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27–45.
(2) For some recent reviews, see: (a) Orru, R.; De Greef, M. *Synthesis* **2003**, 1471–1499. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80. (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980. (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (e) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.
(3) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899–902.
(4) Lin, C.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 6588–6591.
(5) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979–6994.
(6) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, *20*, 1759–1762.
(7) (a) Dardennes, E.; Kovács-Kulyassa, Á.; Renzetti, A.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2003**, *44*, 221–223. (b) Cochard, F.; Laronze, M.; Sigaut, P.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2004**, *45*, 1703–1708. (c) Dardennes, E.; Kovács-Kulyassa, Á.; Boisbrun, M.; Petermann, C.; Laronze, J.-Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1329–1339. (d) Jeannin, L.; Boisbrun, M.; Nemes, C.; Cochard, F.; Laronze, M.; Dardennes, E.; Kovács-Kulyassa, Á.; Sapi, J.; Laronze, J.-Y. *C. R. Chim.* **2003**, *6*, 517–528, and references cited therein.
(8) (a) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723–4724. (b) Lehnert, W. *Tetrahedron* **1972**, *28*, 663–666. (c) Lehnert, W. *Tetrahedron* **1973**, *29*, 635–638. (d) Lehnert, W. *Tetrahedron* **1974**, *30*, 301–305.
(9) (a) Reetz, M. T.; Von Itzstein, M. *J. Organomet. Chem.* **1987**, *334*, 85–90. (b) Reetz, M. T.; Peter, R.; Von Itzstein, M. *Chem. Ber.* **1987**, *120*, 121–122.
(10) (a) Wnuk, S. F.; Lewandowska, E.; Valdez, C. A.; Kinastowski, S. *Tetrahedron* **2000**, *56*, 7667–7671. (b) Noguchi, M.; Yamada, H.; Takamura, S.; Uchida, T.; Hironaka, M.; Kakehi, A.; Yamamoto, H. *Eur. J. Org. Chem.* **2000**, 1489–1496. (c) Hayashi, M.; Nakamura, N.; Yamashita, K. *Tetrahedron* **2004**, *60*, 6777–6783. (d) Yamashita, K.; Tanaka, T.; Hayashi, M. *Tetrahedron* **2005**, *61*, 7981–7985. (e) Zhang, X.-R.; Chao, W.; Chuai, Y.-T.; Ma, Y.; Hao, R.; Zou, D.-C.; Wei, Y.-G.; Wang, Y. *Org. Lett.* **2006**, *8*, 2563–2566.

10.1021/jo800529q CCC: $40.75
Published on Web 08/09/2008

TABLE 1. Trimolecular Condensation and Optimization Studies



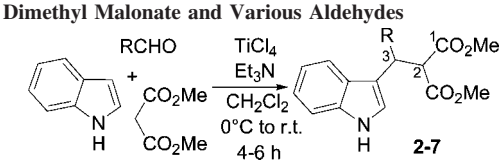
entry	conditions	yield of **1** %[a]
1	$Ti(O\text{-}i\text{-}Pr)_4/Et_3N/CH_2Cl_2$	no reaction
2	$TiCl_4/Et_3N$ (2 equiv)/CH_2Cl_2	46
3	$TiCl_4/Et_3N$/toluene	14
4	$TiCl_4/Et_3N$/THF	traces
5	$TiCl_4/Et_3N/CH_2Cl_2$	81
6	$TiCl_4$/pyridine/CH_2Cl_2	50
7	$ZrCl_4/Et_3N/CH_2Cl_2$	traces
8	$AlCl_3/Et_3N/CH_2Cl_2$	traces
9	$SnCl_4/Et_3N/CH_2Cl_2$	traces

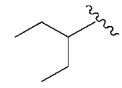
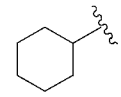
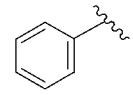
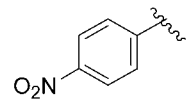
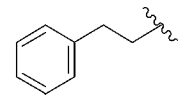
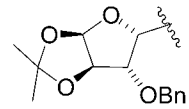
[a] Isolated yield after purification by silica gel chromatography.

Initially, we investigated the reaction between indole, isobutyraldehyde, and dimethyl malonate in dichloromethane in the presence of 1 equiv of titanium tetraisopropoxide and 1 equiv of Et_3N (Table 1).[10d]Unfortunately, we were unable to isolate the corresponding condensation derivative (entry 1). As the $TiCl_4-Et_3N$ reagent system is widely used to generate titanium enolates for applications in aldol and related reactions,[13] we tested this more reactive system in our MCR. We were pleased to find that the trimolecular adduct **1** was isolated in 46% yield using 2 equiv of base in dichloromethane (entry 2). A preliminary optimization was then carried out varying solvent, base, and Lewis acid (entries 3−9). Condensation in the presence of 1 equiv of $TiCl_4$ and Et_3N in toluene proceeded slowly at room temperature, and the yield was only 14% even when the reaction time was increased to 72 h. In the case of pyridine, the adduct was isolated in 50% yield. The use of other strong Lewis acids such as zirconium, aluminum, or tin chlorides did not give the desired product. According to Table 1, the best yield of the trimolecular condensation product was obtained with $TiCl_4/Et_3N$ (1/1 ratio) in CH_2Cl_2 at 0 °C.

To further explore the scope and limitations of this methodology, we tested other aldehydes under optimized conditions (Table 2). Both aliphatic and aromatic aldehydes were used.

TABLE 2. Trimolecular Condensation Promoted by $TiCl_4/Et_3N$ Using Dimethyl Malonate and Various Aldehydes



entry	R	compd	yield %[a]
1		**2**	61
2		**3**	63
3		**4**	54
4		**5**	63
5		**6**	68
6		**7**[b]	66

[a] Isolated yield after purification by silica gel chromatography. [b] Unseparable epimeric (C-3) mixture (60/40).

As shown in Table 2, formation of the corresponding trimolecular adduct proceeded in about 6 h in moderate to good yields (entries 1, 2, and 5). Introduction of an electron-withdrawing group in the para position did not modify the yield significantly (entry 4 vs entry 3), while reaction with a more sensitive aldehyde, derived from D-glucose, afforded **7** as an unseparable mixture (60/40) of two diastereomers (entry 6). From the COSY ^1H NMR spectrum of the mixture **7** we could identify two distinct couplings, $J_{H2-H3} = 7.8$ Hz ($\delta = 4.16$ ppm) and $J_{H2-H3} = 4.7$ Hz ($\delta = 4.09$ ppm), attributed to H-2 protons of the major (**7a**) and the minor (**7b**) diastereomers, respectively. Since chemical shifts and couplings of the sugar moiety remained almost unchanged, the isolated adduct **7** proved to be a C-3 epimeric mixture.[14] The (*S*) absolute configuration of this center in **7a** was determined by analyzing the coupling constants of H-3 ($J_{H6-H7} = 10.3$ Hz, $J_{H7-H7a} = 3.2$ Hz) of **9a**. This latter was obtained via the major alcohol **8a** by debenzylation followed by ^{t}BuOK-mediated lactonization (Scheme 1).

After having tested various aldehydes, 1,3-bifunctional carbonyl derivatives were varied (Table 3). Sterically hindered malonic esters afforded the trimolecular adduct in good yields (entries 1 and 2). Our approach could also be extended to β-ketoester and other active methylene compounds, thus furnishing new applications of the original multicomponent reaction

(11) (a) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577–2580. (b) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047–1048. (c) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174–176. (d) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165–2169. (e) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704. (f) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114. (g) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397–402. (h) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giulani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594–4597. (i) Zou, X.; Wang, X.; Cheng, C.; Kong, L.; Mao, H. *Tetrahedron Lett.* **2006**, *47*, 3767–3771.

(12) For some recent papers, see: (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160–163. (b) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2001**, 347–348. (c) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030–9031. (d) Jørgensen, K. A. *Synthesis* **2003**, 1117–1125. (e) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843–5846. (f) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309–1320. (g) Palomo, C.; Oiarbide, M.; Kardak, B. D.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155. (h) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739–743. (i) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115–2118. (j) Rasappan, R.; Hager, M.; Gissibi, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099–6102. (k) Singh, P. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 1127–1129. (l) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281–2284. (m) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041.

(13) (a) Periasamy, M. *Arkivoc* **2002**, *7*, 152–166. (b) Karunakar, G. V.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 7463–7466, and references cited therein.

(14) Similarly, on the basis of the COSY ^1H NMR spectrum, **20** proved to be a C-3 epimeric mixture, and by analogy, **14** could be considered as well.

SCHEME 1. Determination of the Stereochemistry of 7

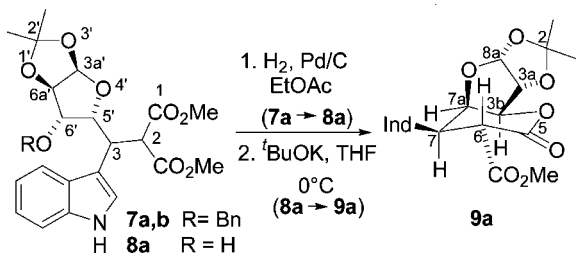
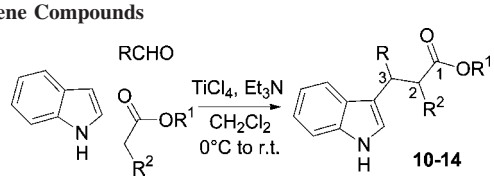
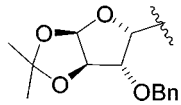


TABLE 3. Condensation of Indole with Aldehydes and Active Methylene Compounds



entry	R	R^1	R^2	compd	yield %[a]
1		Et	CO_2Et	**10**	52
2		*i*Pr	CO_2*i*Pr	**11**	56
3		Me	COMe	**12**[b]	45
4		Et	NO_2	**13**[b]	48
5		Et	$PO(OEt)_2$	**14**[c]	54

[a] Isolated yield after purification by silica gel chromatography. [b] Relative configurations: (2*S**, 3*R**)-**12**; (2*R**, 3*R**)-**13**. [c] Unseparable epimeric (C-3) mixture (50/50).

(entries 3−5). In this way, the use of methyl acetoacetate as active methylene compound gave the corresponding trimolecular condensation product **12** as one diastereomer (entry 3). Similarly, with ethyl nitroacetate we obtained the desired ethyl 2-nitro-3-(3-indolyl)-3-(2-propyl)propanoate **13** as a single diastereomer in 48% yield, offering the possibility to obtain new non-natural β-substituted tryptophans after reduction of the nitro group (entry 4).[15]

The relative stereochemistry (2*R**,3*R**) of **13** was determined by chemical correlation with (2*R**,3*R**)-3-isopropyltryptophan *tert*-butyl ester of known relative configuration,[16,17] according to Scheme 2.

We were delighted to find that the less active triethylphosphonoacetate smoothly reacted with a D-glucose-derived aldehyde and indole affording the corresponding condensation product **14** as an epimeric mixture (entry 5). Its phosphonate

SCHEME 2. Determination of the Relative Configuration of 13

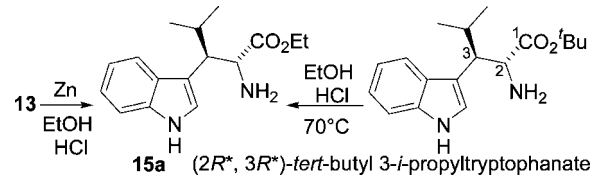
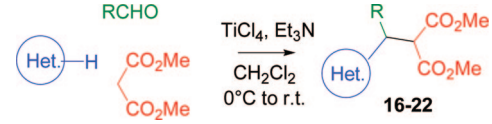
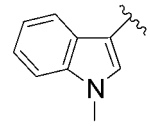
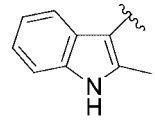
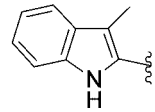
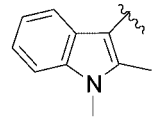
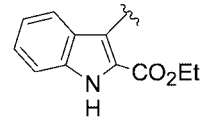
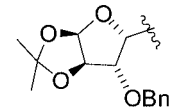
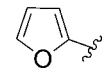
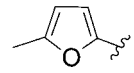


TABLE 4. Extension to Other Heterocyclic Systems



entry	Het	R	compd	yield %[a]
1			**16**	43
2			**17**	45
3			**18**	91
4			**19**	72
5			**20**[b]	66
6			**21**	62
7			**22**	90

[a] Isolated yield after purification by silica gel chromatography. [b] Unseparable epimeric (C-3) mixture (50/50).

function offers the possibility of further transformations by Horner−Emmons-type reactions.

The scope and limitations of this reaction were further investigated by using a variety of structurally different indole and heterocyclic derivatives (Table 4). Both activated (entries 1−4) and unactivated (entry 5) indoles could be used in our titano-promoted trimolecular condensation. Moreover, use of C-3-substituted indole offered the possibility to obtain condensation in the less reactive 2 position (entry 3). Trimolecular adducts between dimethyl malonate, isobutyraldehyde, and furan derivatives could also be obtained in good yields (entries 6 and 7).

(15) During the preparation of the manuscript, a synthesis of β-aryltryptophans based on catalytic Friedel−Crafts alkylation of indoles with aryl nitroacrylates followed by nitro group reduction has appeared: Sui, Y.; Lui, L.; Zhao, J.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron* **2007**, *63*, 5173–5183.

(16) Nemes, C.; Jeannin, L.; Sapi, J.; Laronze, M.; Seghir, H.; Augé, F.; Laronze, J.-Y. *Tetrahedron* **2000**, *56*, 5479–5492.

(17) For comparison, (2*R**,3*S**) 3-Isopropyltryptophan *tert*-butyl ester has also been transformed into the corresponding ethyl ester **15b** (for details, see the Supporting Information).

The mechanism of these reactions probably involves complexation of dimethyl malonate with $TiCl_4$, increasing the acidity of the α hydrogen that can then be easily removed by Et_3N to promote formation of a dark red enolate ion. Attack of this reactive species on the aldehyde generates the Knoevenagel adduct. Finally, the Friedel−Crafts-type alkylation of the heterocyclic system by the alkylidene malonate leads to the trimolecular condensation product. Condensation of indole with isobutyraldehyde and methyl acetoacetate or ethyl nitroacetate gave, after equilibration in the reaction mixture, the diastereomerically pure derivatives (**12** or **13**) bearing isopropyl and ester functions in the anti position.[18] In the case of sugar-derived aldehyde, titanium species may partially dissociate off the activated enolate and chelate the α-alkoxyaldehyde, rendering the Friedel−Crafts reaction less diastereoselective (C-3 epimers: **7**, **14**, **20**).

In conclusion, we have demonstrated the efficiency of the $TiCl_4$−Et_3N reagent system to achieve a trimolecular condensation involving aldehydes, indole, or furan heterocycles and various activated carbonyl compounds in a simple one-pot procedure. Mechanistic and stereochemical aspects of this approach and its extension to the asymmetric Friedel−Crafts reaction of heterocyclic systems using chiral Ti(IV) ligands are currently under investigation.

Experimental Section

General Procedure for the Three-Component Reaction. In a typical procedure, malonester derivative is added to a solution of $TiCl_4$ (1 equiv) in dry dichloromethane (20 mL/10 mmol), at 0 °C, under nitrogen using 3 Å molecular sieves, resulting in the formation of a yellow suspension. After 15 min, Et_3N (1.0 equiv) was added providing a deep red homogeneous solution. A few minutes later, aldehyde (1.0 equiv) was added dropwise, and the mixture was stirred for 1−1.5 h at 0 °C until its disappearance. Finally, heterocycle (1.0 equiv) was added, and the mixture was allowed to warm up to room temperature until the reaction was completed. After quenching by an aqueous solution of 1 M HCl, the organic layer was dried over $MgSO_4$ and concentrated under vacuum to give crude products. Purification by column chromatography on silica gel or by recrystallization furnished the corresponding trimolecular adduct.

Methyl 2-Methoxycarbonyl-3-(3-indolyl)-3-(2-propyl)propanoate 1. Prepared from 1 mL of dimethyl malonate (8.75 mmol), 960 μL of $TiCl_4$, 1.23 mL of Et_3N, 800 μL of isobutyraldehyde and 1.025 g of indole to yield **1** (2.146 g; 81% yield) as a white solid: mp = 128−129 °C; ^{1}H NMR($CDCl_3$) δ 0.86 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.8 Hz), 2.08 (m, 1H), 3.35 (s, 3H), 3.74 (s, 3H), 3.82 (dd, 1H, J = 11.0 Hz, J = 4.8 Hz), 3.99 (d, 1H, J = 11.0 Hz), 7.03 (d, 1H), 7.14 (m, 2H), 7.33 (d, 1H, J = 7.4 Hz), 7.68 (d, 1H, J = 7.6 Hz), 8,08 (sl, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 21.8, 30.5, 42.1, 52.1, 52.6, 56.2, 110.8, 112.8, 119.2, 119.5, 121.7, 122.7, 128.3, 135.5, 168.7, 169.3; IR (KBr) ν 3401, 3048, 2952, 1727, 1432, 1335, 1269, 1150, 1018, 741 cm^{-1}; MS (EI) *m*/*z* 303, 260, 171, 156, 130, 101; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1463.

(2*R,3*R**)-Ethyl 2-nitro-3-(3-indolyl)-3-(2-propyl)propanoate 13:** yield from ethyl nitroacetate (1 mL, 8.75 mmol), $TiCl_4$ (960 μL), Et_3N (1.23 mL), isobutyraldehyde (800 μL), and indole (1.025 g): 1.267 g (48%) as a yellow solid; mp = 124−125 °C; ^{1}H NMR($CDCl_3$) δ 0.90 (d, 3H, J = 6.7 Hz), 0.92 (d, 3H, J = 6.7 Hz), 1.21 (t, 3H, J = 6.9 Hz), 2.14 (m, 1H), 3.99 (dd, 1H, J = 10.1 Hz, J = 5.5 Hz), 4.23 (m, 2H), 5.52 (d, 1H, J = 10.1 Hz), 7.25 (m, 4H), 7.62 (d, 1H, J = 7.5 Hz), 8.18 (sl, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.5, 21.7, 29.9, 43.7, 62.9, 91.3, 110.1, 111.1, 118.9, 119.6, 122.1, 122.9, 128.1, 135.6, 164.3; IR (KBr) ν 3424, 2962, 1754, 1562, 1190, 1018 cm^{-1}; MS (CI) *m*/*z* 305, 259, 172, 141, 82. Anal. Calcd for $C_{16}H_{20}N_2O_4$ (304.34): C, 63.14; H, 6.62; N, 9.20. Found: C, 63.46; H, 6.76; N, 9.13.

Acknowledgment. We thank the French Ministry of Education, Research and Technology for a Ph.D. fellowship to E.D. Financial support from the French Ministry of Foreign Affairs and from the "French-Italian University" to A.R. is gratefully acknowledged. We thank P. Sigaut (MS) and C. Petermann (NMR) for spectroscopic measurements.

Supporting Information Available: General experimental procedures, characterization data, and copies of ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800529Q

(18) Pure **12** and **13** were partially epimerized under kinetic conditions (0 °C, 15 min by treatment with ^{t}BuOK in THF or Et_3N (for details, see the Supporting Information).