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Diastereoselective Synthesis of δ-Aminoacids through Domino Ireland−Claisen Rearrangement and Michael Addition‡

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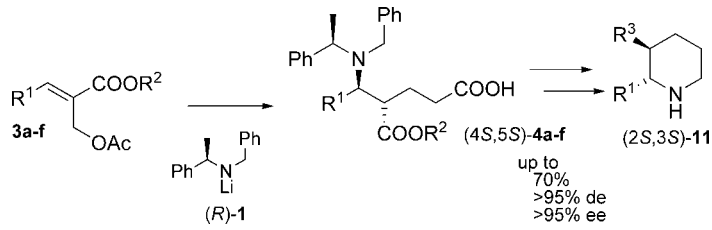
ABSTRACT



A novel domino reaction—stereoselective Ireland−Claisen rearrangement and asymmetric Michael addition—is described. A protocol starting from Baylis−Hillman adducts 3a−f using chiral lithium amide affords optically active γ-substituted δ-aminoacids 4a−f with high diastereoselectivities and enantioselectivities. The acid can be isolated easily from large-scale reactions and transformed to 2,3-disubstituted piperidines 11 or 2-substituted nipecotic acid derivates 12.

The design and development of new asymmetric domino reactions is regarded as a fascinating challenge for organic chemists. The increasing number of publications concerning applications of this type of reaction is testimony to their possibilities in organic synthesis, offering the advantages of atom economy, simple procedures, and savings in cost and time.[1] We have recently demonstrated the asymmetric synthesis of the stereoisomers of 2-amino-5-carboxymethylcyclopentane-1-carboxylate in enantiomerically pure form, via a domino reaction involving an asymmetric Michael addition of chiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**1** to (*E*,*E*)-octa-2,6-diendioate and a subsequent 5-exotrig intramolecular cyclization.[2] Later, the versatility of this methodology was extended, and ϵ and ζ-functionalized α,β-unsaturated esters were shown to participate in conjugate-addition-cyclization reactions.[3] Several domino reactions have been reported, incorporating Michael addition reactions, especially in the initial step. The best-known of these is probably the domino Michael addition-S_N2 reaction also known as the Michael-initiated ring closure (MIRC) reaction;[4] nonetheless, asymmetric Michael-terminated processes are scarce in the literature,[5] as are Claisen rearrangement-initiated domino reactions. A number of these latter have been reported, such as Claisen rearrangement/Bergman cyclization,[6] Claisen rearrangement/Diels−Alder cycload-

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‡ Dedicated to Profesor Miguel Yus in the occasion of his 60th birthday.

(1) (a) For general reviews on domino reactions see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143–2173. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(2) (a) Urones, J. G.; Garrido, N. M.; Díez, D.; El Hammouni, M. M.; Domínguez, S. H.; Casaseca, J. A.; Davies, S. G.; Smith, D. *Org. Biomol. Chem.* **2004**, *2*, 364–372. (b) Urones, J. G.; Garrido, N. M.; Díez, D.; Domínguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1997**, *8*, 2683–2685.

(3) Davies, S. G.; Díez, D.; Domínguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, D. *Org. Biomol. Chem.* **2005**, *3*, 1284–1301.

(4) (a) Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1664–1666. (b) Amputch, M. A.; Matamoros, R.; Little, R. D. *Tetrahedron* **1994**, *50*, 5591–5614.

(5) Ihara, M.; Taniguchi, N.; Suzuki, S.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, 976–977.

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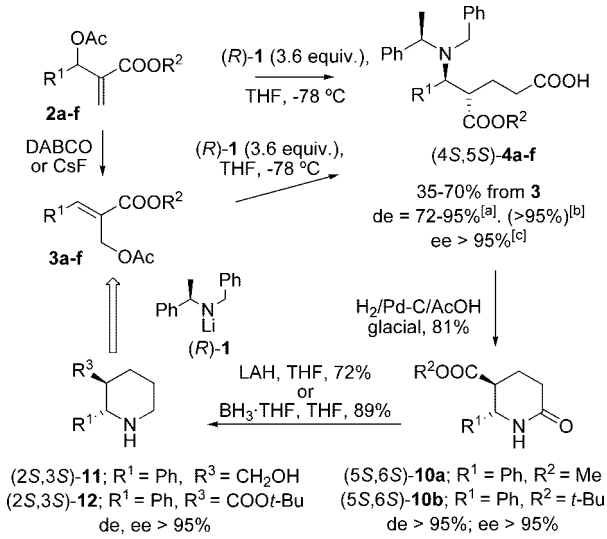
Table 1. Asymmetric Addition of Acetate **2** to (*R*)-**1** (3.6 equiv)

entry	**2**	R^1	R^2	**4**[a] (%)	de[b,c] (%)	**6** (%)	**8** (%)	**9** (%)
1	**a**	phenyl	Me	22	85 (>95)	2	50	2
2	**b**	phenyl	*t*-Bu	24	>95 (>95)		51	
3	**c**	3,4-dimethoxyphenyl	Me	23	86 (>95)	5	27	
4	**d**	pyridin-3-yl	*t*-Bu	37	>95 (>95)	3	29	1
5	**e**	fur-2-yl	Me	18	86 (>95)	5	33	
6	**f**	Ph-CH=CH-	Me			25	6	6

[a] Yields are of isolated product. [b] Determined by ^{1}H NMR spectroscopic analysis, and refer to (4*S*,5*S*)-**4** over (4*R*,5*S*)-**5**, the only δ-amino acid diastereoisomers detected. Even when the minor one could not be totally isolated, it was possible to determine its presence in the chromatography enriched fraction or it could be obtained by base treatment of (4*S*,5*S*)-**4** producing partial epimerisation at C-4. [c] Values in parenthesis after careful column chromatography and in some cases crystallization from EtOAc/hexane.

dition,[7] and Ireland−Claisen rearrangement/Schmittel cyclization.[8] However, we report here the first one-pot highly asymmetric Ireland−Claisen rearrangement/Michael addition domino reaction, which, starting from readily accessible acetylated Baylis−Hillman adducts, yields nonracemic δ-amino acids (Scheme 1). These compounds could find

Scheme 1. Asymmetric Synthesis of γ-Substituted δ-Amino Acids and Transformation to 2,3-Disubstituted Piperidines



[a] Except for **4f** where de = 25%. [b] After chromatography or crystallization from EtOAc/Hexane de > 95%. [c] The ee is consistent with the high optical purity of the lithium amide used.

various applications in organic and peptidomimetic synthesis: for example, as monomers for the generation of oligomers[9] that display a variety of specific secondary structures (named "foldamers" by Gellman),[10] as substituted ethylene dipeptide isosteres,[11] these isomeric peptides show different biological functions,[12] as chiral auxiliaries in asymmetric synthesis,[13] and in the asymmetric synthesis of 2,3-disubstituted piperidines (Scheme 1). Some of these have been the object of considerable synthetic effort, such as for neurokinin-1 (NK_1) receptor antagonists (these are of continuing interest[14] since the natural ligand for the NK_1 receptor, Substance P, has been implicated in the pathophysiology of a wide of disease conditions including neurogenic inflammation, transmission of pain, emesis, and depression[15]) or the potent antimalarial agent (+)-febrifugine,[16] first reported as a metabolite of the Chinese medicinal plant *Dichroa febrifuga*.[17]

Baylis−Hillman adducts have been obtained according to the literature procedure;[18] subsequent acetylation furnishes the acetyl derivatives **2**, which upon isomerization using DABCO[19] or CsF[20] afford the trisubstituted olefins **3** (Scheme 1, Table 1 and 2). We obtained the δ-amino acid **4** by reaction of the above-mentioned acetates with chiral lithium amide (*R*)-**1**, using sequential addition of *n*-butyllithium in tetrahydrofuran at −78 °C to the chiral amine and then adding the acetate (**2** or **3**) in tetrahydrofuran. As shown

(6) Magriotis, P. A.; Kin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2972–2973.

(7) (a) Frank, S. A.; Works, A. B.; Roush, W. R. *Can. J. Chem.* **2000**, *78*, 757–771. (b) Soldermann, N.; Velker, J.; Vallat, O.; Stoeckli-Evans, H.; Neier, R. *Helv. Chim. Acta* **2000**, *83*, 2266–2276.

(8) Yang, Y.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 8545–8549.

(9) Schwalbe, H.; Wermuth, J.; Richter, C.; Szalma, S.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1079–1107.

(10) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (b) Horne, W. S.; Price, J. L.; Keck, J. L.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 4178–4180.

(11) (a) Genest, N.; Lubell, W. D. *J. Pept. Sci.* **2007**, *13*, 355–366. (b) Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2006**, *71*, 4969–4979. (c) Lee, K. W.; Choi, H. W.; Lee, B. H.; Choi, B. S.; Chang, J. H.; Kim, Y. K.; Lee, J. H.; Heo, T. H.; Nam, D. H.; Shin, H. *Synlett* **2005**, *20*, 3136–3138.

(12) Lummis, S. C. R.; Beene, D. L.; Lee, L. W.; Lester, H. A.; Broadhurst, R. W.; Dougherty, D. A. *Nature* **2005**, *438*, 248–252.

(13) Trabocchi, A.; Menchi, G.; Guarna, F.; Machetti, F.; Scarpi, D.; Guarna, A. *Synlett* **2006**, 331–353.

(14) Raubo, P.; Kulagowski, J. J.; Chicchi, G. G. *Synlett* **2006**, 271–274.

(15) Seward, E. M.; Swain, C. J. *Expert Opin. Ther. Pat.* **1999**, *9*, 571–582.

(16) Michael, J. P.; Koning, Ch. B.; Pienaar, D. P. *Synlett* **2006**, 383–386.

(17) Koepfli, J. B.; Brockman, J. A., Jr.; Moffat, J. *J. Am. Chem. Soc.* **1950**, *72*, 3323–3323.

(18) (a) For relevant reviews see : Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Basavaiah, D.; Dharma Rao, P.; Suguna Hymna, R. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Ciganek, E. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, **1997**; Vol 51, p 201.

(19) Mason, P. H.; Emslie, N. *Tetrahedron* **1994**, *50*, 12001–12008.

(20) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403–408.

Table 2. Asymmetric Addition of Acetate **3** to (*R*)-**1** (3.6 equiv)

entry	**3**	R^1	R^2	**4**[a] (%)	de[b,c] (%)	**7** (%)	**8** (%)	**9** (%)
1	**a**	phenyl	Me	54	89 (>95)	3	9	3
2	**b**	phenyl	*t*-Bu	56	>95 (>95)	1	7	2
3	**c**	3,4-dimethoxyphenyl	Me	48	78 (>95)	2	5	7
4	**d**	pyridin-3-yl	*t*-Bu	54	>95 (>95)	2	12	3
5	**e**	fur-2-yl	Me	32	72 (>95)		9	12
6	**f**	Ph-CH=CH-	Me	70	25 (ref 21)		8	8

[a] Yields are of isolated product. [b] Determined by ^{1}H NMR spectroscopic analysis, and refer to (4*S*,5*S*)-**4** over (4*R*,5*S*)-**5**, the only δ-amino acid diastereoisomers detected. Even when the minor one could not be totally isolated, it was possible to determine its presence in the chromatography enriched fraction or it could be obtained by base treatment of (4*S*,5*S*)-**4** producing partial epimerisation at C-4. [c] Values in parenthesis after careful column chromatography and in some cases crystallization from EtOAc/hexane.

in Figure 1 and Table 1, the reaction of acetate **2** in this way gave rise stereoselectively to the diaddition product **8**, together with the acid **4**. However, upon subjecting acetate **3** to the aforementioned conditions, the acid (4*S*,5*S*)-**4** is obtained as the major adduct (de = 72−95%),[21] which could be obtained as a single diastereoisomer by column chromatography or by crystallization either as the δ-amino acid or at a later stage as the δ-lactam (vide infra).

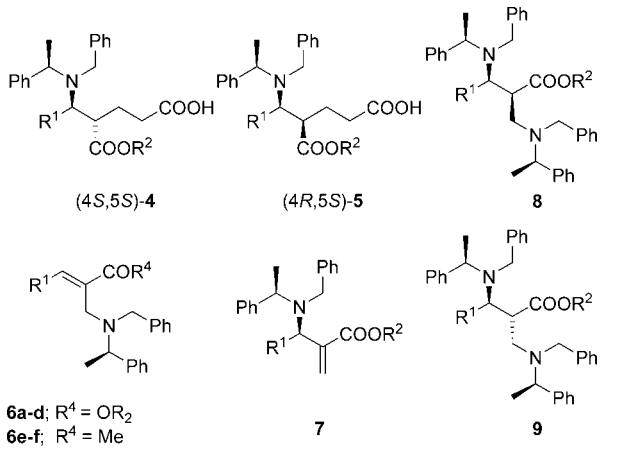


Figure 1. Compounds obtained in the addition of acetates **2** and **3** to (*R*)-**1**, as it is shown in Tables 1 and 2.

Monoaddition adducts **6** and **7** are the result of Michael addition of (*R*)-**1** via an S_N2' protocol to **2** and **3**, respectively, and diaddition adducts **8** and **9**, the result of further addition of the remaining lithium amide to **6** and **7**, respectively. The stereochemistry of monomer and diaddition compounds has been established in a parallel investigation within our group by chemical correlation and ^{1}H NMR including two-dimensional homonuclear COSY, heteronuclear HMQC and HMBC, NOE, and ROESY experiments, and in the case of **8a** by X-ray diffraction structure.

Importantly, the process can be scaled up; even when a mixture of the acetate isomers **2b**/**3b** (5.0 g) in a 1:1 ratio was added to the lithium amide [(*R*)-**1**] as previously described, the crude reaction product was obtained as expected. Upon extraction with NaOH(aq) (1 M) and the usual workup of the acid, **4b** was isolated in a 45% yield, ready to go for further transformation. The nonacidic compounds **7**, **8**, and **9** (Table 1-entry 2, Table 2-entry 2) mentioned previously remained in the organic layer, in 29% overall yield.

In a one-pot reaction, hydrogenolysis of δ-amino acid (4*S*,5*S*)-**4a** and (4*S*,5*S*)-**4b** and subsequent in situ lactamization gave the piperidin-2-ones (5*S*,6*S*)-**10a** ($[\alpha]^{20}_D = +39.7$ ($c = 1.2$, $CHCl_3$) and (5*S*,6*S*)-**10b** ($[\alpha]^{20}_D = +38.1$ ($c = 1.3$, $CHCl_3$), in 81% and 85% yields, respectively. These products crystallize easily from EtOAc/hexane. Reduction of (5*S*,6*S*)-**10a** with LAH in THF furnished piperidine (2*S*,3*S*)-**11** in 72% isolated yield, which illustrates the applicability of the methodology to the preparation of 2,3-disubstituted piperidines. Or, alternatively, reduction of (5*S*,6*S*)-**10b** with BH_3·THF[22] provides compound (2*S*,3*S*)-**12** in 89% yield, keeping the ester functionality and giving access to interesting nipecotic acid derivates.[23] The configuration of the newly formed stereogenic center was determined to be 5*S*,6*S* through single-crystal X-ray structure analysis in the case of product **10a**;[24] the packing of the molecules is shown in Figure 2. This corroborates the anticipated stereochemistry for (4*S*,5*S*)-**4**, assigned taking into account the established model of addition of (*R*)-**1** to (*E*)-α,β-unsaturated esters.[25] Davies et al. have recently published a comprehensive review in this area of chemistry covering the scope, limitations,

(21) (4*S*,5*S*)-**4f** and (4*R*,5*S*)-**4f** can be separated by column chromatography. Interestingly, **2f** and **3f** have been obtained from *trans*-cinnamaldehyde, the only compound used in this work with the carbonyl function not directly attached to the aromatic ring.

(22) Roeske, R. W.; Weitl, F. L.; Prasad, K. U.; Thompson, R. M. *J. Org. Chem.* **1976**, *41*, 1260–1261.

(23) Hoesl, C. E.; Höfner, G.; Wanner, T. *Tetrahedron* **2004**, *60*, 307–318.

(24) Crystal data for (5*S*,6*S*)-**10a**: single crystals were obtained by crystallization from ethyl acetate/hexane. A single crystal of **10a** compound was subjected to X-ray diffraction studies on a Seifert 3003 SC rotating anode diffractometer with (Cu Kα) radiation (graphite monochromator) using 2θ-ω scans at 293(2) K. Crystal data for **10a**: $C_{13}H_{15}N_1O_3$, M = 233.26, triclinic, space group P1 (No. 1), a = 5.7310(11) Å, b = 9.956(2) Å, c = 11.765(2) Å, α = 106.35(3)°, β = 96.43(3)°, γ = 100.74(3)°, V = 623.1(2) Å^3, Z = 2, D_c = 1.243 mg/m^3, m = (Cu Kα) = 0.726 mm^{-1}, F(000) = 248; 1081 reflections were collected at $4.75 \le 2\theta \le 59.85$, of which 1612 with $I > 2\sigma(I)$ were considered to be observed. The structure was determined by direct methods using the SHELXTL suite of programs. Full-matrix least-squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors $R_1 = 0.0441$ and $\omega R_2 = 0.1213$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-608236. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

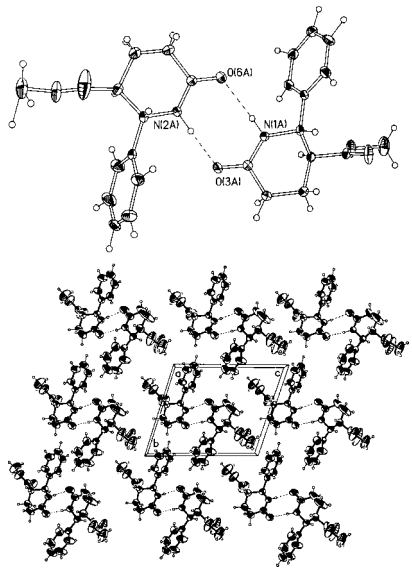
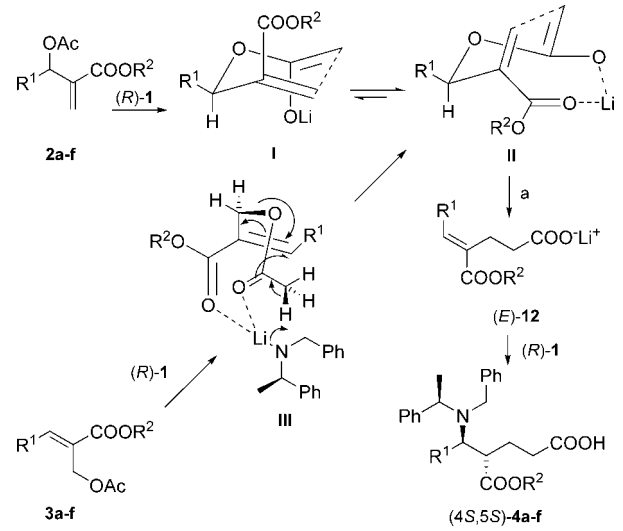


Figure 2. X-ray crystal structure of (5*S*,6*S*)-**10a**.

Scheme 2. Proposed Mechanism To Obtain **4** from **2** and **3**. (a) Ireland−Claisen Rearrangement



and synthetic applications of the use of enantiomerically pure lithium amides as homochiral ammonia equivalents in conjugate addition reactions.[26] Since we can postulate a uniform reaction mechanism, all the examples described should possess the related configuration accordingly.

The crystal contains two molecules in the asymmetric unit. In the crystal structures the molecules of **10a** are connected by intermolecular N−H···O hydrogen bonds [N1···O6 = 2.93(5) Å, H1N···O6 = 2.12(1) Å, <N1−H1N···O6> = 175(7)°; N2···O3 = 2.87(4) Å, H2N···O3 = 1.84(5) Å, <N2−H2N···O3> = 167(3)°]. This demonstrates its potential for peptidomimetic applications.

To explain the stereochemical course of the process that generates **4** from **2** stereoselectively, it is necessary that the Ireland−Claisen rearrangement go through transition state **II**; this should be more stable than TS **I** due to chelation (Scheme 2). This in turn furnishes **12** with the required *E* geometry in the double bond for subsequent asymmetric Michael addition.[25] The high asymmetric induction for stereocenters C-4 and C-5 is in accordance with the reported model for asymmetric Michael addition of (*R*)-**1** to α-alkyl α,*β*-unsasturated ester.[27,25] It is reasonable to think that amide deprotonation is favorable on **3** over initial Michael addition to a trisubstituted double bond, so a rearrangement probably through **III** would give rise **II**[28] and consistently (*E*)-**12** and finally **4**. The difficulty for initial Michael addition on **3**, in relation to **2**, explain his better yield on acid **4**. For acetate **2**, Michael addition to the terminal double bond (which is not very sterically hindered) is preferred over enolate formation. Nonetheless, the solution structure and aggregation of the lithiated chiral enolates remains to be determined.

In conclusion, the novel domino protocol—stereoselective Ireland−Claisen rearrangement and asymmetric Michael addition—provides the first practical and efficient one-pot route to optically active *γ*-substituted *δ*-amino acids. In two examples, hydrogenolysis has been proven to produce the parent piperidin-2-ones, 2-substituted nipecotic acid derivates, and 2,3-disubstituted piperidines upon concomitant reduction. Importantly, the analogous series of reactions deploying the enantiomer of lithium amide (*R*)-**1** in the initial conjugate addition step will allow simple access to *ent*-**4**, and consequently to (2*R*,3*R*)-**11**. The highly enantioenriched title compounds now available in this way are valuable substrates for further synthetic transformations to polyamino natural products and 2,3-disubstituted chiral piperidines, which are currently being investigated in our laboratory.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999–2008.

(26) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.

(27) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153–1154.

(28) To our knowledge, this is the first example of *O*,*O*-allylic rearrangement followed by Claisen rearrangement and Michael addition, promoted by lithium amide. The allylic acetate rearrangement is well documented in basic medium (see refs 17 and 18), with Pd(II) (see Overman, L. E. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 579–586) or TMSOTf as catalyst (see Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis*, **2001**, 545–548). For anionic *O*,*N*-carbamate allylic rearrangement see ref 18.