Pergamon

Tetrahedron Letters 43 (2002) 2627–2631

TETRAHEDRON LETTERS

Diene-transmissive hetero Diels–Alder reaction of cross-conjugated azatrienes with ketenes: a novel and efficient, stereo-controlled synthetic method for hexahydroquinolinones

Takao Saito,* Satoru Kobayashi, Masato Ohgaki, Mari Wada and Chikako Nagahiro

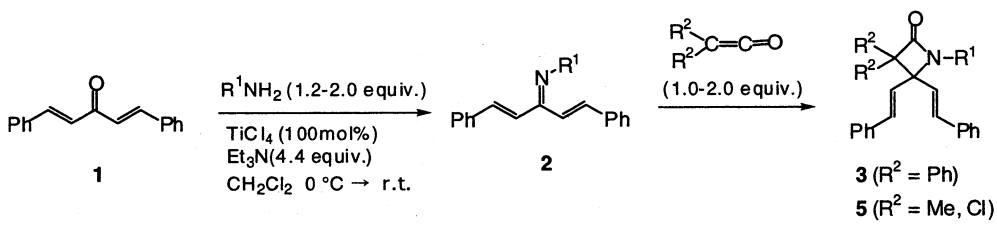
Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 26 December 2001; revised 4 February 2002; accepted 8 February 2002

Abstract—The cross-conjugated azatrienes, *N*-aryl-, *N*-alkyl- or *N*-dimethylamino-diβ-styrylmethanimines, reacted with diphenylketene and dimethylketene at room temperature to afford [2+2] cycloadducts, while the reaction with dichloroketene produced [4+2] cycloadducts. Upon heating, the [2+2] cycloadducts underwent a [1,3] sigmatropic rearrangement giving the formal [4+2] cycloadducts. The second Diels–Alder reaction of the [4+2] mono-adducts with electron-deficient dienophiles such as tetracyanoethylene, *N*-phenylmaleimide and methyl vinyl ketone gave hexahydroquinolinone derivatives stereoselectively. The cross-conjugated azatriene bearing different substituents at β- and β′-positions also underwent the diene-transmissive hetero Diels–Alder reaction in a highly site-, regio- and stereo-selective manner.

The hetero Diels–Alder (HDA) methodology is among the most attractive and important tools for the synthesis of a wide range of six-membered heterocyclic compounds because of their potentially powerful and straightforward construction of heterocycles with high control of regio- and stereochemistry.[1] On the other hand, the diene-transmissive hetero Diels–Alder (DTHDA) reaction should offer an efficient method for synthesis of, especially, ring-fused heterocycles by performing multi-domino (hetero) DA reactions in a stereo-controlled manner.[2–4,†]

In this context, we have recently reported the first examples of the DTHDA reaction of cross-conjugated azatrienes **2**.[5] This process involved the initial aza DA cycloaddition of **2** with a reactive dienophile, tosyl isocyanate, followed by the second DA reaction with some representative dienophiles to give stereoselectively ring-fused pyrimidinone derivatives as bis-adducts in good yields.[5] Unfortunately, the azatrienes **2** having an R^1 group on the nitrogen such as Ph, *p*-Tol, $PhCH_2$, *i*-Pr, and a quite effective electron-releasing Me_2N group, failed to react with representative dienophiles



Scheme 1.

Keywords: diene-transmissive Diels–Alder reaction; domino/tandem reactions; cycloaddition; quinoline; nitrogen heterocycle.

* Corresponding author. Tel.: +81-(0)3-5228-8254; fax: +81-(0)3-3235-2214; e-mail: tsaito@ch.kagu.sut.ac.jp

† Although the diene-transmissive Diels–Alder (DTDA) reaction is formally considered to be a set of multi-sequential DA reactions of α,ω-divinylpoly(vinylidene), the DTHDA reaction can usually be defined by two sequential (so-called tandem, domino, etc.) cycloadditions of the two final processes that involve an initial DA reaction of a cross-conjugated triene (or its equivalents) with a dienophile, followed by a second DA cycloaddition on the newly-formed, transmitted diene unit of the mono-adduct with a dienophile to give a bis-adduct, where one or more heteroatoms are contained within either a triene framework or a dienophile skeleton or both. For DTDA reactions of carbotrienes, see the literature in Ref. 2.

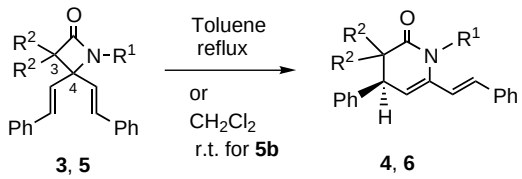
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00303-9

such as tetracyanoethylene, *N*-phenylmaleimide, maleic anhydride, dimethyl fumarate, dimethyl acetylenedicarboxylate, ethyl vinyl ether and styrene under, if necessary, harsh conditions and/or in the presence of a Lewis acid promoter.[6,‡] In order to gain further insight into the cycloaddition mechanism and to extend this DTHDA methodology, we reasoned to utilize ketenes as a useful carbon–carbon dienophile in the initial cycloaddition of **2** and a new variant **9** because of their isoelectronic property with isocyanates.

When azatriene **2a** (*N*-phenyldiβ-styrylmethanimine, $R^1=Ph$), generated in situ from the reaction of the corresponding ketone **1** with aniline by the action of the reagents $TiCl_4$ and Et_3N, was allowed to react with diphenylketene at 0°C for 5 min, a 1:1-adduct was obtained in 98% yield, the structure of which was assigned to be a [2+2] cycloadduct **3a** on the basis of spectroscopic data (Scheme 1). The other aryl, benzyl, alkyl and dimethylamino-substituted R^1-azatrienes, **2b–e**, also reacted with diphenylketene to give the [2+2] cycloadducts **3b–e** in good yields. The results are summarized in Table 1. The formation of the [2+2] cycloadducts was not unexpected but, unfortunately, the diene-transmissive Diels–Alder methodology would not be applicable with the structure **3**.

Many instances are available in the literature that ketenes reacted with imines, even with conjugated imines, to afford azetidinones (β-lactams) as [2+2] cycloadducts,[9] whereas it is also reported that selected 1-azadienes (conjugated imines) underwent [4+2] cycloaddition with ketenes.[1,8,10,11] So, we subjected the cycloadduct **3a** to thermal reaction. When **3a** was heated in refluxing toluene for 2 h, it was found that the dihydropyridone derivative **4a** as the formal [4+2] cycloadduct was quantitatively obtained, which was presumably formed by a [1,3] sigmatropic rearrangement with the cleavage of the C(3)-C(4) bond of the azetidinone ring in **3a** (Scheme 2).[12] Similarly, the [2+2] cycloadducts **3b–e** were converted exclusively to the [4+2] cycloadducts **4b–e** (Table 1, runs 2–5). Dimethylketene generated in situ from the acid chloride precursor also reacted with the azatriene **2e**, which is relatively stable and isolable, to afford the [2+2] cycloadduct **5a** in good yield, which was similarly converted to the [4+2] cycloadduct **6a** quantitatively upon heating (run 6). However, the reaction with dichloroketene generated gave **6b** in low yield instead of **5b** even if performed at a low temperature (run 7). The periselection outcome for the latter reaction is in accord with the precedent observation that generated haloketene tends to give [4+2] cycloadducts in Diels–Alder reactions with 1-azadienes.[9,13]

With the mono-cycloadducts (**4** and **6**) in hand, we performed the second cycloaddition with some representative electrophilic dienophiles, since the mono-cycloadducts have an aminodiene unit and hence normal electron-demanding DA reactions are anticipated to proceed smoothly. First, the reactions of **4** with a symmetrical, simple dienophile, tetracyanoethylene (TCNE), were carried out to see the π-facial selectivity. As expected, the reactions proceeded rapidly (in 5–10 min) at room temperature in CH_2Cl_2 to



Scheme 2.

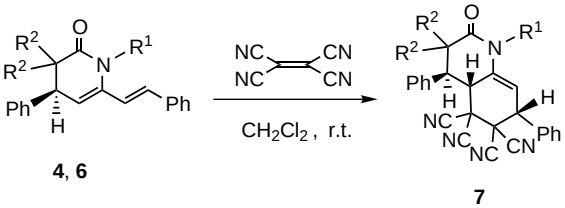
Table 1. Reaction of azatrienes **2** with ketenes and thermal conversion of [2+2]cycloadducts **3** and **5** to [4+2]cycloadducts **4** and **6**

Run	R^1	R^2	Azatriene	[2+2]Cycloadduct	Yield (%) (**1**→**3**)	[4+2]Cycloadduct	Yield (%)
1	Ph	Ph	**2a**	**3a**	98	**4a**	99
2	*p*-$CH_3OC_6H_4$	Ph	**2b**	**3b**	84	**4b**	99
3	Benzyl	Ph	**2c**	**3c**	76	**4c**	99
4	*i*-Pr	Ph	**2d**	**3d**	90	**4d**	99
5	Me_2N	Ph	**2e**	**3e**	91	**4e**	99 (93)[a]
6	Me_2N	Me	**2e**	**5a**	96	**6a**	96
7	Me_2N	Cl	**2e**	**5b**	–	**6b**	(23)[a]

[a] In parentheses, yield in a one-pot reaction from **2e**.

‡ The results were not surprising because this would be the case as often encountered by such limitation that 1-aza-1,3-butadienes are usually (inherently) less reactive as a 4π-component in DA reaction unless they bear sufficiently electron-donating or electron-withdrawing group(s) at (a) suitable position(s) of the azadiene system.[1,7] Moreover, semi-empirical calculations (AM1) have revealed that both of the coefficients on the terminal nitrogen (1), carbon (4) and (4′) atoms in the HOMO of **2** ($R^1=Ph$) are considerably small (N: −0.28 and C: 0.20, 0.06, respectively) in the normal electron-demanding HOMO diene-LUMO dienophile DA reaction predicted by the magnitude differences of MOs energy level separations and that the net atomic charges on the nitrogen atom (−0.16) of **2** and the cumulene carbon (0.49) of tosyl isocyanate were relatively large in the negative and positive signs, respectively.[6] These findings suggest that the reaction with tosyl isocyanate proceeds stepwise rather than in a concerted manner.[8] This assumption is consistent with the theoretical prediction that TCNE possessing lower LUMO energy than that of TsNCO should have reacted with **2**, if it is a concerted reaction, and with the fact that the reaction of **2** (particularly when $R^1=NMe_2$) with TCNE did not give any cycloadducts.

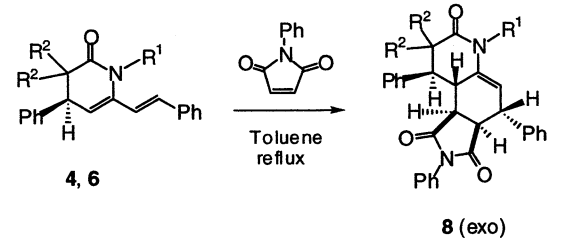
give the [4+2] cycloadducts **7**[14] in excellent yields with complete π-facial selectivity (Scheme 3, Table 2). The stereochemistry of **7** suggests that the dienophile should cycloadd from the less hindered backside of the diene **4**/**6** (*syn* to H at the 4-position of the pyridone ring) due to the steric reason (vide infra). Next, we carried out the reactions with *N*-phenylmaleimide to examine the *endo–exo* selectivity as well as the π-facial selectivity (Scheme 4). The reactions proceeded upon heating in toluene under reflux for 6–20 h to quantitatively yield the [4+2] cycloadducts **8** with almost complete *exo* selectivity except for the case of R^2=Me. The results are summarized in Table 3. The stereochemistry of **8** was determined ^{1}H NMR spectroscopically (Fig. 1). Particularly, a large vicinal coupling constant (JH_{1-2}= 12.4 Hz) was observed between H_1 and H_2, which indicates a *trans*-diaxial relationship between them, and hence the attack of the dienophile from the bottom side (Fig. 2). Nuclear Overhauser effect (NOE) was observed notably between H_1 and H_3, and H_2 and H_5, in a *cis*-relationship and no NOE between H_2 and H_3, and H_4 and H_5, suggesting a *trans* (diaxial) relationship and hence the *exo* addition of the dienophile. The *exo* addition was also supported by a relatively large coupling constant (8.12 Hz) between H_4 and H_5, implying a *trans*-relationship. Fig. 2 shows the *exo* and *endo* orientations. The fact that the observed vicinal coupling



Scheme 3.

Table 2. DA Reaction of **4** and **6** with TCNE to give hexahydroquinolinones **7**

Run	Diene	Cycloadduct	Yield (%)
1	**4a**	**7a**	99
2	**4b**	**7b**	99
3	**4c**	**7c**	99
4	**4d**	**7d**	99
5	**4e**	**7e**	99
6	**6a**	**7f**	94
7	**6b**	**7g**	99



Scheme 4.

Table 3. DA Reaction of **4** and **6** with *N*-phenylmaleimide to give pyrroloquinolines **8**

Run	Diene	Cycloadduct	*exo*:*endo*[a]	Yield (%)
1	**4a**	**8a**	>95:5	99
2	**4b**	**8b**	>95:5	99
3	**4c**	**8c**	>95:5	99
4	**4d**	**8d**	>95:5	99
5	**4e**	**8e**	>95:5	99
6	**6a**	**8f**	69:31	94
7	**6b**	**8g**	>95:5	99

[a] Ratio determined by ^{1}H NMR (300 or 400 MHz) spectroscopy. No *endo* isomers were detected for a ratio of >95:5.

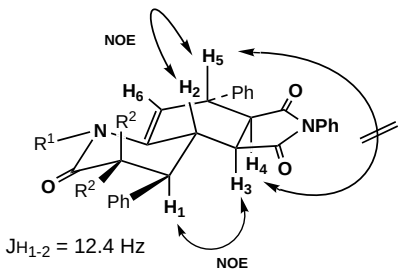


Figure 1. NOE measurement of **8a** (*exo*).

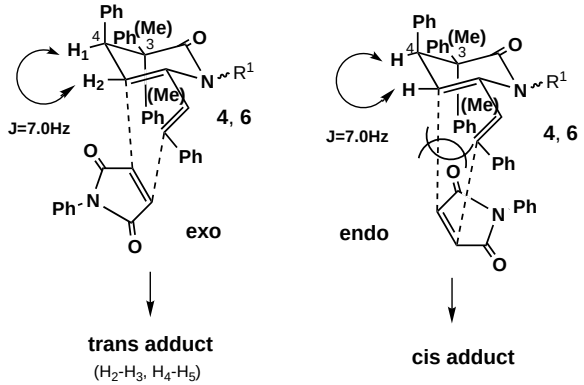
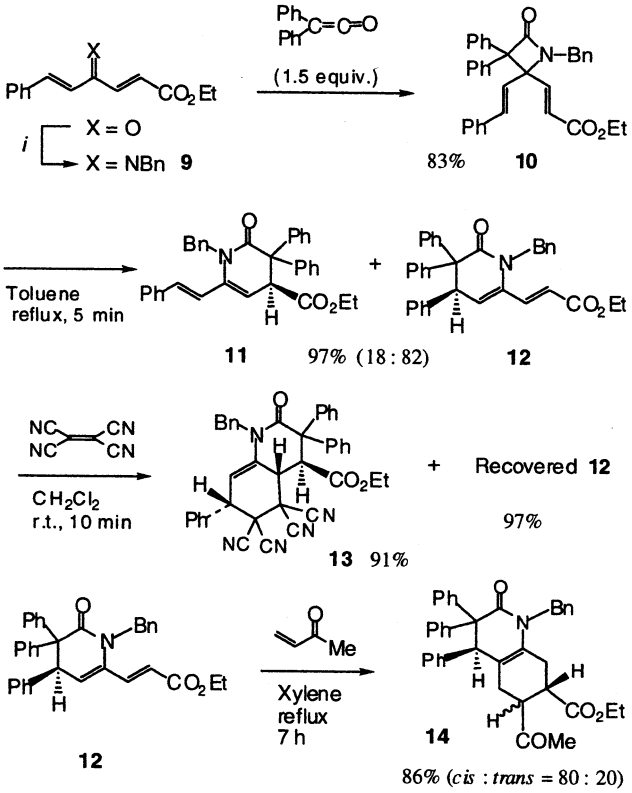


Figure 2. *exo* and *endo* orientations.

constant between H_1 and H_2 in the diene **4**/**6** was ca. 7 Hz, suggests a quasi-equatorial arrangement of H_1 and, consequently, the phenyl group at the 4-position being in quasi-axial orientation. The dienophile, therefore, cycloadded exclusively from the bottom side to avoid the steric hindrance between the phenyl group and the dienophile in attacking from the topside. In the *endo* addition, the steric repulsion with the CO moiety of the dienophile exerted by the axial phenyl or chloro group at the 3-position, would be large enough to surpass the second orbital interaction, while the less bulky methyl group would allow the *endo* addition by preference of 31% (Table 3, run 6). It is noteworthy that low *exo–endo* selectivity was observed in the second cycloaddition of *N*-phenylmaleimide with the initial [4+2] mono-cycloadducts of **2** with tosyl isocyanate.[5] This is probably due to the absence of an axial substituent on the nitrogen at the 3-position in the initial cycloadducts.



Scheme 5. (*i*) Bn–NH_2 (2 equiv.), $TiCl_4$ (100 mol%), Et_3N (4.4 equiv.), CH_2Cl_2, 0°C→rt.

The new azatriene **9**, generated in situ from the corresponding ketone, reacted with diphenylketene rapidly to afford the [2+2] cycloadduct **10** in an 83% yield (Scheme 5). Heating the adduct **10** at 111°C for 5 min caused the [1,3] rearrangement to give a mixture of two pyridones **11** and **12** in 97% yield with a ratio of 18:82, which are formally the [4+2] cycloadducts of the azatriene **9** reacting at both cross-conjugated diene sites. It should be pointed out that the [4+2] cycloadduct **12** arising from the reaction at the electron-rich diene moiety of **9** is the major product. When the mixture of **11** and **12** was allowed to react with TCNE at room temp. for 10 min, the quinolone derivative **13** was obtained only as the [4+2] cycloadduct from **11** in 91% yield together with the unreacted **12** in 97% yield. Interestingly, the recovered **12** reacted with methyl vinyl ketone in refluxing xylene for 7 h giving compound **14** in 86% yield with a *cis*:*trans* ratio of 80:20 which was presumably formed by 1,3-H-migration of the preformed *endo* and *exo* [4+2] cycloadducts, respectively.

In conclusion, the diene-transmissive hetero Diels–Alder methodology of cross-conjugated azatrienes with ketenes provides a new entry to stereoselective synthesis of quinoline derivatives.

References

1. (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; (b) Boger, D. L. In *Comprehensive Organic Synthesis*; Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Oxford: Pergamon, 1991; Vol. 5, p. 451; (c) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1; (d) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099 and references cited therein.
2. For DT(H)DA of carbotrienes: (a) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 81; (b) Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, 239; (c) Tsuge, O.; Kanemasa, S.; Wada, E.; Sakoh, H. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 756 and references cited therein; (d) Tsuge, O.; Hatta, T.; Yakata, K.; Maeda, H. *Chem. Lett.* **1994**, 1833; (e) Spino, C.; Liu, G. *J. Org. Chem.* **1993**, *58*, 817; (f) Spino, C.; Tu, N. *Tetrahedron Lett.* **1994**, *35*, 3683; (g) Hosomi, A.; Masunari, T.; Tominaga, Y.; Yanagi, T.; Hojo, M. *Tetrahedron Lett.* **1990**, *31*, 6201; (h) Adam, W.; Deufel, T.; Finzel, R.; Griesbeck, A. G.; Hirt, J. *J. Org. Chem.* **1992**, *57*, 3991; (i) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013; (j) Woo, S.; Squire, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573.
3. For DTHDA of thiatrienes: (a) Motoki, S.; Matsuo, Y.; Terauchi, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 284; (b) Saito, T.; Kimura, H.; Sakamaki, K.; Karakasa, T.; Moriyama, S. *Chem. Commun.* **1996**, 811.
4. For DTHDA of oxatrienes: (a) Tsuge, O.; Hatta, T.; Yoshitomi, H.; Kurosaka, K.; Fujiwara, T.; Maeda, H.; Kakehi, A. *Heterocycles* **1995**, *41*, 225; (b) Tsuge, O.; Hatta, T.; Fujiwara, T.; Yokohari, T.; Tsuge, A. *Heterocycles* **1999**, *50*, 661; (c) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596; (d) Spino, C.; Liu, G. *J. Org. Chem.* **1993**, *58*, 817.
5. For DTHDA of azatrienes: Saito, T.; Kimura, H.; Chonan, T.; Soda, T.; Karakasa, T. *Chem. Commun.* **1997**, 1013.
6. Saito, T.; Kobayashi, S.; Chonan, T.; Yoshida, S.; Wada, M. 30th Congress of Heterocyclic Chemistry, Hachioji, Abstr. 1L-06, P. 22, 1999; unpublished results.
7. (a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713; (b) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075; (c) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261; (d) Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557; (e) Sakamoto, M.; Satoh, K.; Nagano, M.; Nagano, M.; Tamura, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3389; (f) Sakamoto, M.; Nagano, M.; Suzuki, Y.; Tamura, O. *Tetrahedron* **1996**, *52*, 733; (g) Blanco, M. M.; Alonso, M. A.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1996**, *52*, 5933 and references cited therein.
8. (a) Tietze, L. F.; Fennen, J.; Geissler, H.; Schulz, G.; Anders, E. *Liebigs Ann. Chem.* **1995**, 1681; (b) Fabian, W. M. F.; Kollenz, G. *J. Phys. Org. Chem.* **1994**, *7*, 1; (c) Elliot, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron Lett.* **1998**, *39*, 8911.
9. Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p. 85 and references cited therein.

10. (a) Elliott, M. C.; Monk, A. E.; Kruiswijk, E.; Hibbs, D. E.; Jenkins, R. L.; Jones, D. V. *Synlett* **1999**, 1379; (b) Sakamoto, M.; Miyazawa, K.; Kuwabara, K.; Tomimatsu, Y. *Heterocycles* **1979**, *12*, 231; (c) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499; (d) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245; (e) Ohshiro, Y.; Komatsu, M.; Uesaka, M.; Agawa, T. *Heterocycles* **1984**, *22*, 549.
11. For a recent, excellent paper on the cycloaddition mechanism of ketenes with cyclic and acyclic carbodienes giving [4+2]- or [2+2]cycloadducts, see: Machiguchi, T.; Hasegawa, T.; Ishiwata, A.; Terashima, S.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1999**, *121*, 4771.
12. Rossi, E.; Abbiati, G.; Pini, E. *Tetrahedron* **1999**, *55*, 6961.
13. (a) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499; (b) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245.
14. Compound **7a**: colorless crystals, mp 195–197°C; IR (KBr):1696, 1650, 1496, 1280, 700 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$) δ 4.10 (ddd, $J=1.9$, 2.1, 10.9, 1H, H-2), 4.29 (dd, $J=1.9$, 4.8, 1H, H-3), 4.92 (d, $J=10.9$, 1H, H-1), 5.10 (dd, $J=2.1$, 4.8, 1H, H-4), 6.67–7.74 (m, 25H, Ar); FABMS 632 (M^++H, 6), 246 (17), 185 (60), 93 (100). FABHRMS calcd for $C_{43}H_{30}N_5O$ [M^++H]: 632.2450. Found: 632.2443.