

HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 305 - 311. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd June, 2010, Accepted, 26th July, 2010, Published online, 27th July, 2010
DOI: 10.3987/COM-10-S(E)66

**SYNTHESIS OF 2,3,4-TRI-SUBSTITUTED 3,4-DIHYDRO-
QUINAZOLINES VIA TANDEM NUCLEOPHILIC ADDITION/EPOXY
RING-OPENING CYCLIZATION METHODOLOGY USING
N-(2-OXIRANYLPHENYL)CARBODIIMIDES WITH NUCLEOPHILES[†]**

**Takao Saito,* Tatsuya Ote, Masahiro Shiotani, Hiroko Kataoka, Takashi
Otani, and Noriki Kutsumura**

Department of Chemistry, Faculty of Science, Tokyo University of Science,
Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan. tsaito@rs.kagu.tus.ac.jp

Abstract – *N*-(2-Oxiranylphenyl)carbodiimides, which were synthesized *via* an aza-Wittig reaction of the corresponding functionalized iminophosphanes with aromatic and aliphatic isocyanates, underwent O-, S-, C-, or N-nucleophilic addition onto a cumulene, followed by an epoxy ring-opening cyclization with the newly formed NH-nucleophile in a one-pot reaction to furnish 2,3-disubstituted 4-(hydroxymethyl)-3,4-dihydroquinazolines in a highly stereospecific manner.

We have been interested in the chemistry of functionalized (conjugated) heterocumulenes such as carbodiimides, and their use as key substrates for the synthesis of nitrogen heterocycles.¹ Considerable advances in the chemistry have been made.² For examples, the synthetic approaches used included an aza-Wittig reaction of iminophosphanes with isocyanates to generate functionalized carbodiimides, followed by the use of various ring-forming transformations such as (a) electrocyclization,^{1a-c,3} (b) intra-^{1b-d,4} or (c) intermolecular Diels-Alder type reaction,^{1a,c,5} and (d, e) various types of cyclizations (various bond-forming reactions, *e.g.*, nucleophilic addition/substitution,^{1e-g,3a,6} and Pauson-Khand reaction^{1h-j,7}) in tandem with the heterocumulene functionality and adjacent available functional group, to furnish nitrogen heterocycles **A** (Chart 1). Our ongoing program to develop a useful synthetic method based on this concept of a functionalized carbodiimide-mediated, tandem annulation strategy for

[†]This paper is dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday.

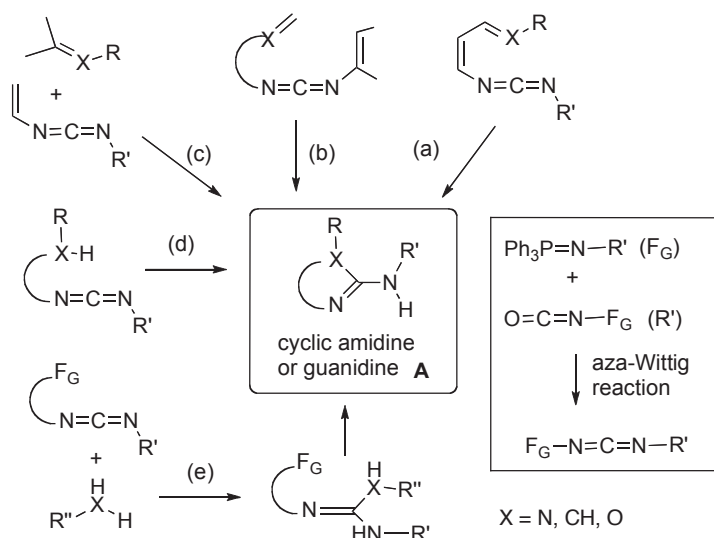
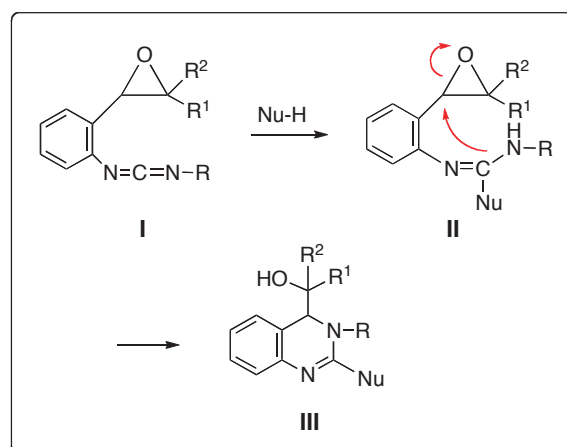


Chart 1 Various tandem cyclization pathways leading to cyclic amidines or guanidines

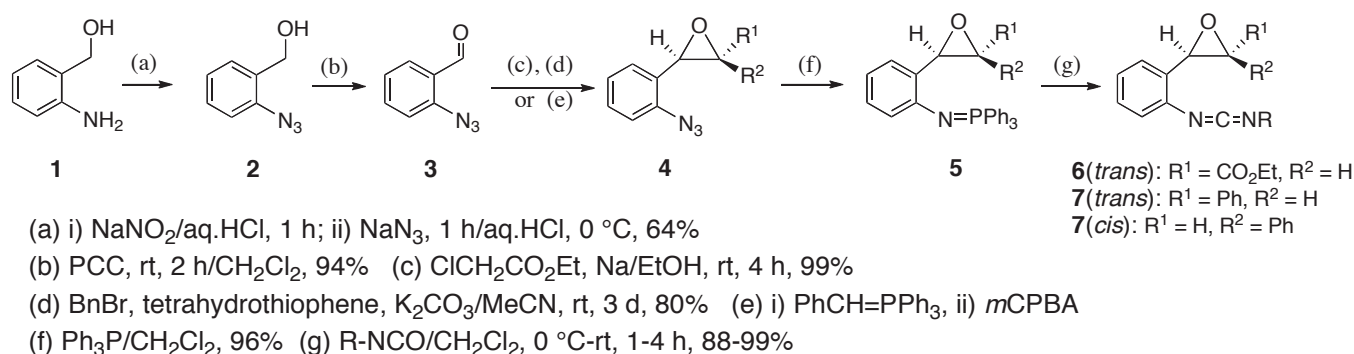


Scheme 1. Tandem nucleophilic addition/epoxy ring-opening cyclization

heterocyclic synthesis prompted us to seek a suitable new functional group that could play an important part in the ring-forming reaction in tandem.

Scheme 1 depicts our new strategy. A nucleophile initially adds to the cumulene carbon of the (2-oxiranylphenyl)carbodiimide **I** to give the intermediate **II**, the newly formed NH-nucleophilic center, which subsequently attacks the epoxy ring resulting in a ring-opening cyclization in a permitted 6-exo-tet manner to produce 4-(hydroxymethyl)dihydroquinazoline **III**. Herein, we report the results of this new synthetic approach to dihydroquinazolines having a β -amino-alcohol unit.

First, the key substrates **6-7**, epoxy-carbodiimides bearing a variety of substituents (R, R¹, R²), were prepared from *o*-aminobenzyl alcohol (**1**) according to the route shown in Scheme 2.

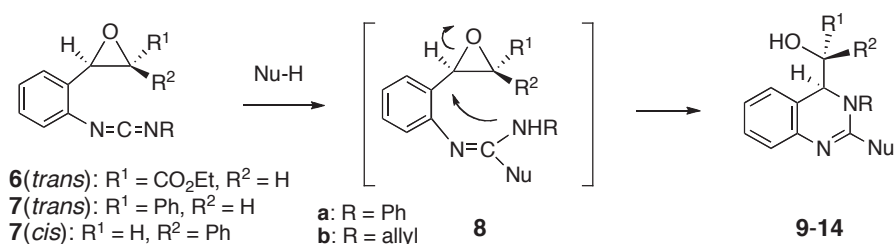


Scheme 2. Preparation of the oxiranylcarbodiimides **6-7**

Oxiranylcarbodiimides **6-7** obtained in this way were allowed to react initially with alcohol nucleophiles; the results are summarized in Table 1. The reaction with methanol or *o*-chlorophenol in the presence of the corresponding sodium alcoholate or phenolate proceeded slowly to afford the dihydroquinazolines **9**

and **10/10'** in good to moderate yields (Table 1, runs 1–6).⁸ The presence of the base is necessary because the reaction without the base did not proceed even at 110 °C for 10 h. We believe that the reaction is initiated by nucleophilic addition onto the cumulene bond to form the intermediate **8**, followed by the intramolecular nucleophilic attack at the proximal epoxy ring by the newly formed amine nucleophile, with simultaneous epoxy ring-opening to produce the dihydroquinazolines **9** and **10/10'**. The exclusive formation of the *erythro*-isomer from *trans*-**6/7** and *threo*-isomer from *cis*-**7** confirms that the

Table 1. Reaction of carbodiimides **6-7** with O-, S- and C-nucleophiles to give dihydroquinazolines **9-14**



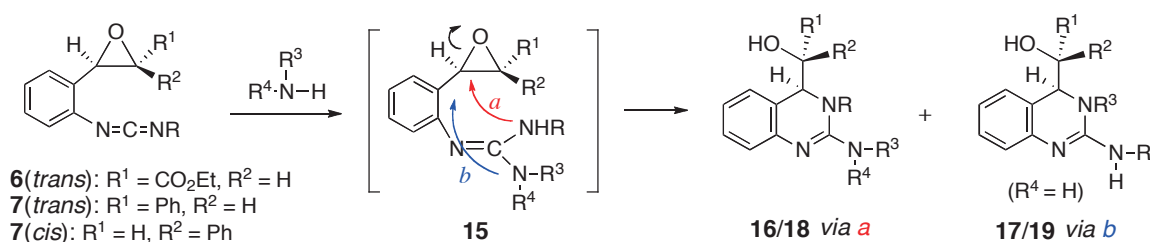
Run	Carbo-diimide	R ¹	R ²	R	Nu-H	Base (equiv)	Reaction Conditions	Product ^a (Yield/%)
1	6a	CO ₂ Et	H	Ph	MeOH	MeONa (0.1)	rt, 3 d, CH ₂ Cl ₂	9a (61)
2	6b	CO ₂ Et	H	allyl	MeOH	MeONa (0.2)	rt, 48 h, CH ₂ Cl ₂	9b (37)
3	6a	CO ₂ Et	H	Ph	<i>o</i> -ClPhOH	Na (1.0)	rt, 2 h, CH ₂ Cl ₂	9c (54)
4	7a	Ph	H	Ph	MeOH	MeONa (0.1)	0 °C→rt, 5 d, CH ₂ Cl ₂	10a (66)
5	7a	Ph	H	Ph	<i>o</i> -ClPhOH	Na (1.0)	0 °C→rt, 5 d, CH ₂ Cl ₂	10b (44)
6	7a (<i>cis</i>)	H	Ph	Ph	MeOH	MeONa (0.1)	0 °C→rt, 6 h, MeOH	10'a (85)
7	6a	CO ₂ Et	H	Ph	C ₁₂ H ₂₅ SH	Et ₃ N (1.0)	0 °C, 1 h, CH ₂ Cl ₂	11a (82)
8	6b	CO ₂ Et	H	allyl	C ₁₂ H ₂₅ SH	Et ₃ N (1.0)	0 °C, 10 min, CH ₂ Cl ₂	11b (67)
9	6a	CO ₂ Et	H	Ph	PhSH	-	0 °C, 10 min, CH ₂ Cl ₂	11c (96)
10	7a	Ph	H	Ph	C ₁₂ H ₂₅ SH	Et ₃ N (1.0)	0 °C→rt, 1 h, CH ₂ Cl ₂	12a (82)
11	7a	Ph	H	Ph	PhSH	-	0 °C→rt, 24 h, CH ₂ Cl ₂	12b (85)
12	7a (<i>cis</i>)	H	Ph	Ph	C ₁₂ H ₂₅ SH	Et ₃ N (1.0)	0 °C→rt, 2 h, MeOH	12'a (90)
13	6a	CO ₂ Et	H	Ph	NCCH ₂ CO ₂ Et	NaH (1.0)	-78→-40 °C, 1 h, THF	13a (98)
14	6a	CO ₂ Et	H	Ph	MeCOCH ₂ COMe	NaH (1.0)	-78°C→rt, 2 h, THF	13b (60)
15	7a	Ph	H	Ph	NCCH ₂ CO ₂ Et	NaH (1.0)	-78→0 °C, 10 min, THF	14a (76)
16	7a (<i>cis</i>)	H	Ph	Ph	NCCH ₂ CO ₂ Et	NaH (1.0)	-78 °C →rt, 30 min, THF	14'a (89)

^a A prime mark for the products **10'** and **12'** denotes *threo*-isomer. For the others (**9-12**), *erythro*-isomers.

intramolecular nucleophilic substitution in the epoxy ring-opening process proceeded with complete inversion of the stereogenic center at the epoxy-2-position. Similarly, the oxiranylcabodiimides **6-7** also

reacted with dodecanethiol and benzenethiol to afford the dihydroquinazolines **11** and **12/12'** stereospecifically in good yields (runs 7–12).⁸ It is noteworthy that the reaction with benzenethiol proceeded even in the absence of an amine base (Et₃N) (runs 9 and 11). The reaction with carbon nucleophiles was also examined. Treatment with Grignard reagents RMgBr (R = Me, *n*-Hex, Ph) or enolate anions derived from acetonitrile and acetophenone failed. However, reaction with stable enolate anions derived from 1,3-diketones successfully resulted in the formation of the expected C-attacking quinazoline products **13** and **14/14'** (runs 13–16).

Table 2. Reaction of carbodiimides **6-7** with N-nucleophiles to give dihydroquinazolines **16-19**



Run	Carbo-diimide	R ¹	R ²	R	R ³ R ⁴ N-H	Reaction Conditions	Product ^a (Yield/%)
1	7a (<i>cis</i>)	H	Ph	Ph	piperidine	0 °C, 10 min, CH ₂ Cl ₂	16'a (78)
2	7b	Ph	H	allyl	piperidine	0 °C, 10 min, CH ₂ Cl ₂	16b (33) ^b
3	7c	Ph	H	<i>p</i> -Tol	allylNH ₂	0 °C, 1 h, CH ₂ Cl ₂	16c (75)
4	7d	Ph	H	<i>p</i> -ClPh	allylNH ₂	0 °C, 10 min, CH ₂ Cl ₂	16d (66)
5	7e	Ph	H	<i>c</i> -Hex	allylNH ₂	0 °C, 1 h, CH ₂ Cl ₂	17e (42) ^b
6	7f	Ph	H	allyl	<i>c</i> -HexNH ₂	0 °C, 1 h, CH ₂ Cl ₂	16f [= 17e] (64)
7	7a (<i>cis</i>)	H	Ph	Ph	allylNH ₂	0 °C, 10 min, CH ₂ Cl ₂	16'g (93)
8	7e (<i>cis</i>)	H	Ph	<i>c</i> -Hex	allylNH ₂	rt, 2 h, CH ₂ Cl ₂	17'e (99)
9	7f (<i>cis</i>)	H	Ph	allyl	<i>c</i> -HexNH ₂	0 °C, 30 min, CH ₂ Cl ₂	16'f [= 17'e] (72)
10	6a	CO ₂ Et	H	Ph	allylNH ₂	rt, 10 min, CH ₂ Cl ₂	18a (99)
11	6a	CO ₂ Et	H	Ph	<i>c</i> -HexNH ₂	rt, 30 min, CH ₂ Cl ₂	18b (85)
12	6b	CO ₂ Et	H	allyl	PhNH ₂	114 °C, 3 h, toluene	19a [= 18a] (30)
13	6b	CO ₂ Et	H	allyl	<i>c</i> -HexNH ₂	rt, 1 h, CH ₂ Cl ₂	18c (45)
14	6c	CO ₂ Et	H	<i>c</i> -Hex	allylNH ₂	rt, 3 h, CH ₂ Cl ₂	19c [= 18c] (60)
15	6d	CO ₂ Et	H	<i>p</i> -ClPh	allylNH ₂	rt, 10 min, CH ₂ Cl ₂	18d (80)

^a A prime mark for the products **16'** and **17'** denotes *threo*-isomer. For the others (**16-19**), *erythro*-isomers.

^b Yield for the reaction performed in one-pot from corresponding azide **4**.

The carbodiimides **7a**(*cis*) and **7b** reacted rapidly with a secondary amine, piperidine, at 0 °C for 10 min to give the corresponding dihydroquinazolines **16'a** and **16b**, respectively, in fairly good yield (Table 2,

runs 1–2). The reaction apparently proceeded through the guanidine intermediate **15**, in which an epoxy ring-opening cyclization *via* path “a” by NHR attack was involved. The reaction of carbodiimides **7c**, **7d** and **7a**(*cis*) (R = aryl) and **7f** and **7f**(*cis*) (R = allyl) with a primary amine (R⁴ = H: allyl amine, cyclohexyl amine) also produced the corresponding quinazolines **16c**, **d**, **f** and **16’f**, **g** similarly *via* the path “a” in **15** with the ambidentate nucleophilic guanidines (runs 3, 4, 6, 7 and 9). In contrast, the reaction of carbodiimides **7e** and **7e**(*cis*) bearing a bulky substituent (R = cyclohexyl group) with a less bulky allyl amine yielded quinazolines **17e** and **17’e** *via* the alternative path “b” by NHR³ attack in **15** (runs 5 and 8). Similarly, the reaction of *trans*-[(3-ethoxycarbonyloxyran-2-yl)phenyl]carbodiimides **6a–d** with a primary amine (allyl amine, cyclohexyl amine, aniline) resulted in the formation of quinazolines **18** or **19** (runs 10–15). The preferred formation of either **16/18** or **17/19**⁹ may be ascribed principally to the steric hindrance of the NHR(R³) group rather than to its nucleophilicity,¹⁰ if the allyl group is relatively bulkier than a phenyl group under the conditions in **15**.

In summary, we have developed the functionalized carbodiimide-mediated tandem nucleophilic addition /epoxy ring-opening cyclization method for stereospecific synthesis of 2,3-disubstituted 4-(hydroxymethyl)-3,4-dihydroquinazolines.

REFERENCES AND NOTES

1. (a) T. Saito, M. Nakane, M. Endo, H. Yamashita, Y. Oyamada, and S. Motoki, *Chem. Lett.*, 1986, 135; (b) T. Saito, H. Ohmori, E. Furuno, and S. Motoki, *J. Chem. Soc., Chem. Commun.*, 1992, 22; (c) T. Saito, T. Ohkubo, H. Kuboki, M. Maeda, K. Tsuda, T. Karakasa, and S. Satsumabayashi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3065; (d) T. Saito, H. Ohmori, T. Ohkubo, and S. Motoki, *J. Chem. Soc., Chem. Commun.*, 1993, 1802; (e) S. Hirota, R. Kato, M. Suzuki, Y. Soneta, T. Otani, and T. Saito, *Eur. J. Org. Chem.*, 2008, 2075; (f) S. Hirota, T. Sakai, N. Kitamura, K. Kubokawa, N. Kutsumura, T. Otani, and T. Saito, *Tetrahedron*, 2010, **66**, 653; (g) T. Saito and K. Tsuda, *Tetrahedron Lett.*, 1996, **37**, 9071; (h) T. Saito, N. Furukawa, and T. Otani, *Org. Biomol. Chem.*, 2010, **8**, 1126; (i) T. Saito, M. Shiotani, T. Otani, and S. Hasaba, *Heterocycles*, 2003, **60**, 1045; (j) T. Saito, K. Sugizaki, T. Otani, and T. Suyama, *Org. Lett.*, 2007, **9**, 1239; and references cited therein.
2. For reviews see, (a) P. Molina and M. J. Vilaplana, *Synthesis*, 1994, 1197; (b) P. M. Fresneda and P. Molina, *Synlett*, 2004, 1; (c) S. Eguchi, *ARKIVOC*, 2005, (ii), 98; (d) S. Eguchi, *Top. Heterocycl. Chem.*, 2006, **6**, 113; (e) F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, and J. M. de los Santos, *Tetrahedron*, 2007, **63**, 523.
3. (a) J. Barluenga, M. Ferrero, and F. Palacios, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2193; (b) P. Molina, J. Alcantara, and C. Lopez-Leonardo, *Tetrahedron*, 1997, **53**, 3281.
4. (a) M. Alajarin, P. Molina, and A. Vidal, *J. Nat. Prod.*, 1997, **60**, 747; (b) K. Nagamatsu, A. Serita,

- J.-H. Zeng, H. Fujii, N. Abe, and A. Kakehi, *Heterocycles*, 2006, **67**, 337; (c) C. Shi, Q. Zhang, and K. K. Wang, *J. Org. Chem.*, 1999, **64**, 925; (d) X. Lu, J. L. Petersen, and K. K. Wang, *J. Org. Chem.*, 2002, **67**, 7797; (e) M. Schmittl, J.-P. Steffen, D. Rodriguez, B. Engelen, E. Neumann, and M. E. Cinar, *J. Org. Chem.*, 2008, **73**, 3005, and references cited therein.
5. (a) T. Okawa, N. Osakada, S. Eguchi, and A. Kakehi, *Tetrahedron*, 1997, **53**, 16061; (b) H. Wamhoff and A. Schmidt, *J. Org. Chem.*, 1993, **58**, 6976; (c) M. A. Arnold, K. A. Day, S. G. Duron, and D. Y. Gin, *J. Am. Chem. Soc.*, 2006, **128**, 13255.
6. (a) T. Okawa, M. Kawase, S. Eguchi, A. Kakehi, and M. Shiro, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2277; (b) M. Noguchi, H. Okada, M. Watanabe, K. Okuda, and O. Nakamura, *Tetrahedron*, 1996, **52**, 6581; (c) P. Molina, M. Alajarin, and A. Vidal, *Tetrahedron*, 1989, **45**, 4263; (d) J. M. Quintela, R. Alvarez-Sarandes, M. C. Veiga, and C. Peinador, *Heterocycles*, 1997, **45**, 1319; (e) J.-F. Zhao, C. Xie, S.-Z. Xu, M.-W. Ding, and W.-J. Xiao, *Org. Biomol. Chem.*, 2006, **4**, 130.
7. (a) C. Mukai, T. Yoshida, M. Sorimachi, and A. Odani, *Org. Lett.*, 2006, **8**, 83; (b) D. Aburano, T. Yoshida, N. Miyakoshi, and C. Mukai, *J. Org. Chem.*, 2007, **72**, 6878.
8. The structures **9-14** were determined spectroscopically. **12a** (Table 1, run 10): Colorless oil; ^1H NMR (CDCl_3 , 500.0 MHz) δ 0.87 (t, J = 6.9 Hz, 3H), 1.25-1.35 (m, 18H), 1.56-1.63 (m, 2H), 2.44 (brs, 1H, OH), 2.93 (ddd, J = 6.9, 8.1, 12.9 Hz, 1H), 3.19 (ddd, J = 6.6, 8.1, 12.9 Hz, 1H), 4.55 (d, J = 6.8 Hz, 1H, H-4), 4.75 (d, J = 6.8 Hz, 1H, CH-O), 6.64-6.66 (m, 2H, Ar), 6.72 (d, J = 7.4 Hz, 1H, Ar), 6.99 (dt, J = 1.2, 7.4 Hz, 1H, Ar), 7.13-7.15 (m, 3H, Ar), 7.21 (d, J = 7.8 Hz, 1H, Ar), 7.26-7.35 (m, 6H, Ar). ^{13}C NMR (CDCl_3 , 125.6 MHz) δ 14.1 (CH_3), 22.6 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 69.7 (CH, C-4), 74.2 (CH, C-O), 122.0 (C), 123.2 (CH, Ar), 123.8 (CH, Ar), 126.7 (CH, Ar), 127.0 (2CH, Ph), 127.1 (CH, Ar), 127.4 (2CH, Ph), 127.9 (CH, Ar), 128.2 (2CH, Ph), 128.7 (2CH, Ph), 128.8 (CH, Ar), 140.3 (C, Ph), 142.6 (C, Ph), 143.9 (C), 158.7 (C). IR (neat): 3401, 3062, 2923, 2854, 2360, 1527, 1481, 1257 cm^{-1} . ESI-MS: Calcd for $\text{C}_{33}\text{H}_{43}\text{N}_2\text{OS}$ ($\text{M} + \text{H}$) $^+$ 515.3096, found 515.3107. **12'a** (Table 1, run 12): Colorless oil; ^1H NMR (CDCl_3 , 600.1 MHz): δ 0.87 (t, J = 7.0 Hz, 3H), 1.25-1.30 (m, 16H), 1.35-1.39 (m, 2H), 1.62-1.67 (m, 2H), 2.72 (brs, 1H, OH), 2.94 (ddd, J = 6.8, 8.2, 12.9 Hz, 1H), 3.24 (ddd, J = 6.3, 8.2, 13.0 Hz, 1H), 4.62 (d, J = 8.4 Hz, 1H, H-4), 4.69 (d, J = 8.4 Hz, 1H, CH-O), 6.12 (d, J = 7.4 Hz, 1H), 6.75 (ddd, J = 2.0, 6.5, 7.4 Hz, 1H, Ar), 7.02 (d, J = 7.0 Hz, 2H, Ph), 7.17-7.23 (m, 6H, Ar), 7.31 (dd, J = 7.5, 8.0 Hz, 2H, Ph), 7.46 (d, J = 7.8 Hz, 2H, Ph). ^{13}C NMR (CDCl_3 , 150.9 MHz): δ 14.1 (CH_3), 22.7 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 69.8 (CH, C-4), 74.3 (CH, C-O), 122.0 (C), 123.2 (CH, Ar), 123.8 (CH, Ar), 126.7 (CH, Ar), 127.0 (2CH, Ph), 127.1 (CH, Ar), 127.4 (2CH, Ph), 127.9 (CH, Ar), 128.2 (2CH, Ph), 128.7 (2CH, Ph), 128.8 (CH, Ar), 140.0 (C, Ph),

142.4 (C, Ph), 144.8 (C), 157.3 (C). IR (neat): 3216, 3062, 2923, 2854, 2360, 1527, 1481, 1257 cm^{-1} . ESI-MS: Calcd for $\text{C}_{33}\text{H}_{42}\text{N}_2\text{NaOS}$ ($\text{M} + \text{Na}$)⁺ 537.2916, found 537.2909.

9. The structures **16-19** were determined spectroscopically (in particular, the observed correlation for NOESY and HMBC measurements between H-4/HC(Ar-N(3)) and H-4/C-N(3), respectively).
10. Similar observations and arguments have been reported. See lit.^{1f} and G. Blanco, N. Segui, J. M. Quintela, C. Peinador, M. Chas, and R. Toba, *Tetrahedron*, 2006, **62**, 11124.