HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 227 - 235. © The Japan Institute of Heterocyclic Chemistry
Received, 24th March, 2008, Accepted, 21st April, 2008, Published online, 24th April, 2008. COM-08-S(N)55

DIENE-TRANSMISSIVE HETERO-DIELS–ALDER CYCLOADDITION USING CROSS-CONJUGATED DIOXATRIENES: A NOVEL SYNTHESIS OF TETRAHYDROPYRAN-FUSED AZA- AND THIA-HETEROCYCLES

Takao Saito,* Satoru Kobayashi, Takashi Otani, Hideoki Iwanami, and Takayuki Soda

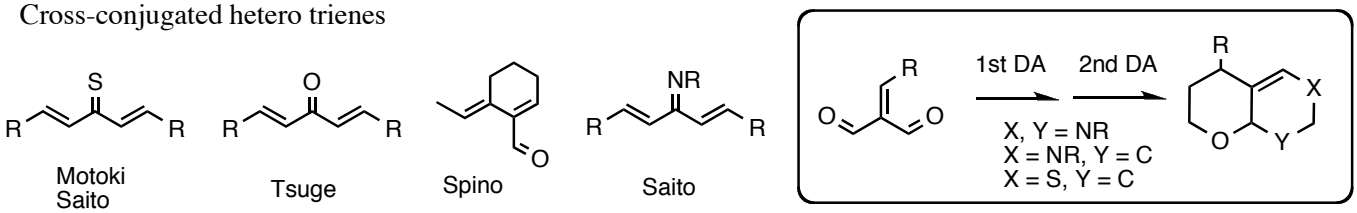
Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan. tsaito@rs.kagu.tus.ac.jp

This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Abstract – The diene-transmissive hetero-Diels–Alder methodology using cross-conjugated dioxatrienes [2-(*R*-methylene)propanedials] has been developed. The initial cycloaddition with electron-rich dienophiles, followed by the reactions of the resulting 1-oxadiene moiety of the monoadducts with amines and Lawesson's reagent generated 1-azadienes and 1-thiadienes. The second hetero-Diels–Alder reaction of these reactive heterodienes with dienophiles (tosyl isocyanate, diphenylketene, enones, and maleinimide) produced pyran-fused aza- and thiaheterocycles, providing a new synthetic method for these heterocycles.

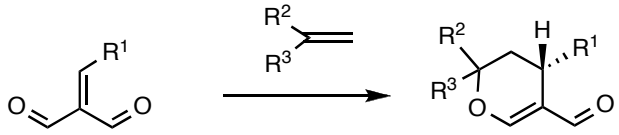
Sequential (tandem, domino, or cascade)[1] transformation methodologies are efficient, valuable, and elegant means for organic synthesis. The Diels–Alder (DA) reaction is one of the most useful and important tools for the synthesis of a wide range of six-membered cyclic compounds because it gives a straightforward and potentially powerful construction of such products with predictable and highly controlled regio- and stereochemistry.[2] Therefore, sequential methodologies involving such cycloaddition reactions in the procedure[1f,g,k] are useful and attractive tools for the highly regio- and stereocontrolled synthesis of cyclic compounds. The diene-transmissive Diels–Alder (DTDA) reaction represents one of these tandem cycloaddition–transformation methods.[3] Tsuge, Kanemasa, and Wada et al. and other groups have developed this DTDA methodology using cross-conjugated carbotrienes and equivalents capable of double 4π participation for the synthesis of bicyclo[3.3.0]decene systems.[4] However, a very limited number of examples of the diene-transmissive hetero-Diels–Alder (DTHDA) methodology have

been reported so far, despite its high potential for the construction of ring-fused heterocyclic systems.[5–10] The first reported examples of the DTHDA reaction included that of cross-conjugated thiatrienes.[5,6] Tsuge et al.[7] and Spino et al.[8] independently demonstrated cross-conjugated oxatriene–DTHDA reactions. We previously reported that cross-conjugated azatrienes also took part in the DTHDA reaction in the synthesis of quinolinone, quinazolinone, and pyrimidopyridazinone derivatives.[9,10] In these DTHDA methodologies the cross-conjugated heterotrienes contain only one heteroatom; sulfur, oxygen, or nitrogen, in each framework. No published report has appeared so far on a DTHDA reaction of cross-conjugated trienes that contains two or more heteroatoms in the skeleton. Herein, we report that cross-conjugated dioxatrienes [2-(*R*-methylene)propanedials] participate in the DTHDA cycloaddition for synthesis of pyran-fused pyrimidine, pyridine, and thiopyran derivatives.



Because 2-(R^1-methylene)propanedials (**1**) are anticipated to undergo an inverse electron-demand hetero-Diels–Alder cycloaddition behaving as 1-oxabutadiene of a 4π-component activated by the other

Table 1. Initial HDA cycloaddition of **1** with electron-rich dienophiles.



1 **2**

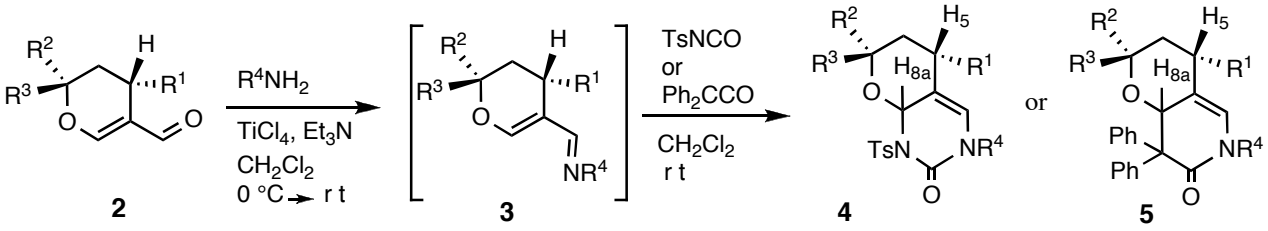
Entry	**1**	R^1	R^2	R^3	Method[a]	Adduct	Yield / %	*Cis:trans* (R^1–R^2)
1	**1a**	AcNH	Ph	Ph	A	**2a**	69	–
2	**1a**		Ph	H	A	**2b**	40	55:45
3	**1a**		EtO	H	B	**2c**	99	58:42
4	**1b**	AcO	EtO	H	C	**2d**	75	70:30
5	**1c**	BzO	EtO	H	C	**2e**	67	65:35
6	**1d**	Ph	Ph	Ph	A	**2f**	42	–
7	**1e**	*p*-Tol	Ph	Ph	D	**2g**	50	–
8	**1e**		Ph	H	D	**2h**	44	77:23
9	**1e**		EtO	H	B	**2i**	43	80:20

[a] Method A: 30 mol% of BF_3•OEt_2, room temp., 13–22 h, CH_2Cl_2. Method B: 50 mol-fold excess of ethyl vinyl ether, reflux in CH_2Cl_2, 1 h. Method C: one-pot reaction from triformylmethane, room temp., in CH_2Cl_2, 40 h for **2d**, 50 °C, 1 h for **2e**. Method D: 100 mol% of $ZnCl_2$, room temp., 0.5–2 h, CH_2Cl_2.

formyl group, the initial cycloaddition with 1,1-diphenylethene, styrene, and ethyl vinyl ether were carried out.

When the reaction of 2-(acetylaminomethylene)propanedial (**1a**)[11] with 1,1-diphenylethene was performed in refluxing toluene for 10 h, the corresponding [4 + 2] cycloadduct **2a**[12] was obtained in only 7% yield together with recovery of **1a** (54%). However, reaction in the presence of BF_3•OEt_2 (Method A) produced **2a** in 69% yield (Table 1, Entry 1). Similarly, the BF_3•OEt_2-promoted reaction of **1a** with styrene gave the cycloadduct **2b** in 40% yield with 55:45 ratio of *cis*/*trans* isomers (Entry 2). With ethyl vinyl ether (excess amount) the reaction of **1a** readily proceeded in refluxing dichloromethane for 1 h (Method B) to quantitatively produce the cycloadduct **2c** in 58:42 ratio of *cis/trans* isomers (Entry 3). 2-(Acetyloxy- and benzoyloxymethylene)propanedials (**1b**,**c**),[13] generated by the acylation of triformylmethane, also reacted with ethyl vinyl ether in a one-pot reaction to give the cycloadducts **2d**,**e** in good yields with *cis:trans* ratios of 70:30–65:35 (Method C, Entries 4 and 5). 2-(Arylmethylene)propanedials (**1d**,**e**)[14] both reacted readily with 1,1-diphenylethene in the presence of 30 mol% of BF_3•OEt_2 (Method A) or 100 mol% of $ZnCl_2$ (Method D) in dichloromethane at room temperature to yield cycloadducts **2f** (42%) and **2g** (50%), respectively (Entries 6 and 7). Also, **1e** reacted with styrene and ethyl vinyl ether to produce *cis*(*endo*)-selectively **2h** (44%) and **2i** (43%), respectively (Entries 8 and 9).

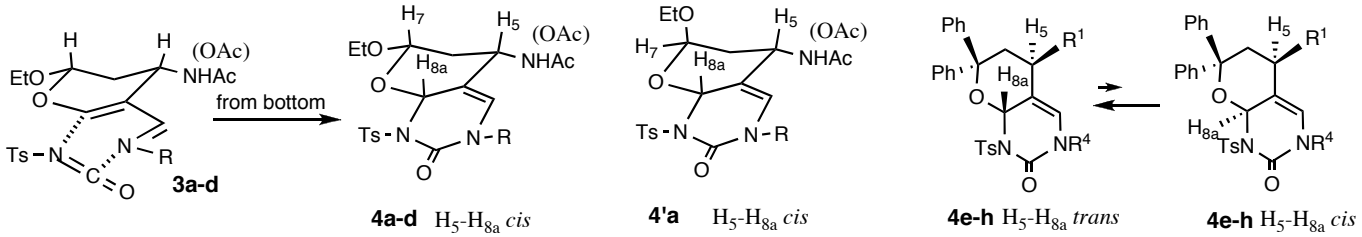
Table 2. Generation and second HDA cycloaddition of azadienes **3** with TsNCO.



Entry	**2**	R^1	R^2	R^3	R^4	Azadiene	Adduct	Yield[a] / %	*Cis:trans* (H_5–H_{8a})[b]
1	**2c** (*cis*)[c]	AcNH	EtO	H	*p*-$MeOC_6H_4$	**3a**	**4a**	70[c]	> 95:5
	2c (*trans*)[c]	AcNH	H	EtO	*p*-$MeOC_6H_4$	**3′a**[d]	**4′a**[d]	63[c]	> 95:5
2	**2d** (*cis*)	AcO	EtO	H	$PhCH_2$	**3b**	**4b**	58	> 95:5
3	**2d** (*cis*)	AcO	EtO	H	Me_2N	**3c**[e]	**4c**	94	> 95:5
4	**2e** (*cis*)	BzO	EtO	H	Ph	**3d**	**4d**	46	> 95:5
5	**2f**	Ph	Ph	Ph	*p*-ClC_6H_4	**3e**	**4e**	79	20:80
6	**2f**	Ph	Ph	Ph	*i*-Pr	**3f**	**4f**	62	47:53
7	**2g**	*p*-Tol	Ph	Ph	Me_2N	**3g**[e]	**4g**	88	60:40
8	**2g**	*p*-Tol	Ph	Ph	*i*-Pr	**3h**	**4h**	66	45:55
9	**2f**	Ph	Ph	Ph	*p*-Tol	**3i**	**5**	99	72:28

[a] Isolated yield. [b] *Cis:trans* ratio determined based on ^{1}H NMR integration. Ratio > 95:5 denotes that no minor *trans* isomer was detected. [c] A mixture of isomers with *cis:trans* = 58:42 was used. Yields based on each isomer. [d] A prime mark in **3′** and **4′** denotes a *trans* relationship between the R^1 and R^2 groups. [e] Isolated (64% and 99% from *cis*-**2d** and **2g**, respectively).

The obtained monoadducts **2** having a transmitted 1-oxadiene 4π-moiety are not sufficiently reactive towards dienophiles such as vinyl ethers, maleinimides, acrylates, and TCNE, but it was found that the formyl group that activated in the initial HDA could be readily converted to imine and thiocarbonyl functions. Thus, 1-azadienes **3** generated from **2** by treatment with amines in the presence of $TiCl_4$–Et_3N were subjected to the second hetero-Diels–Alder reaction in a one-pot reaction with a reactive dienophile, TsNCO, to produce [4 + 2] cycloadducts, pyrano[2,3-*d*]pyrimidines **4**[15] in fair to good yield (Table 2). In the cases of entries 1–4, the reactions are highly diastereo π-face-selective; only *cis*-isomers (H_5–H_{8a}, based on NOESY) of **4a–d** and **4′a** were formed and they did not isomerize even in refluxing benzene-d_6. These facts suggest that the dienophile (TsNCO) attacked the azadiene from the bottom side to give *cis*-isomers (H_5–H_{8a}) of **4a–d** and **4′a**, as shown in Scheme 1. In contrast, the reactions of azadienes **3e–h** produced cycloadducts **4e–h** in good yields with low *cis:trans* selectivity and in addition, the ratios were not reproducible (entries 5–8). ^{1}H NMR monitoring of the isomers (e.g., **4g**) revealed that in refluxing benzene-d_6 the *cis:trans* ratio of 67:33 for the isomers changed to 22:78 after 1.5 h and that in the presence of some silica gel in $CDCl_3$ at room temperature, **4g** in a *cis:trans* ratio of 60:40 was completely converted into the single *trans* isomer of **4g** after one day. These facts imply that *cis*-**4e–h** are apt to isomerize into the thermodynamically more stable *trans*-isomers and that the ratios for **4e–h** are not kinetically controlled ratios.



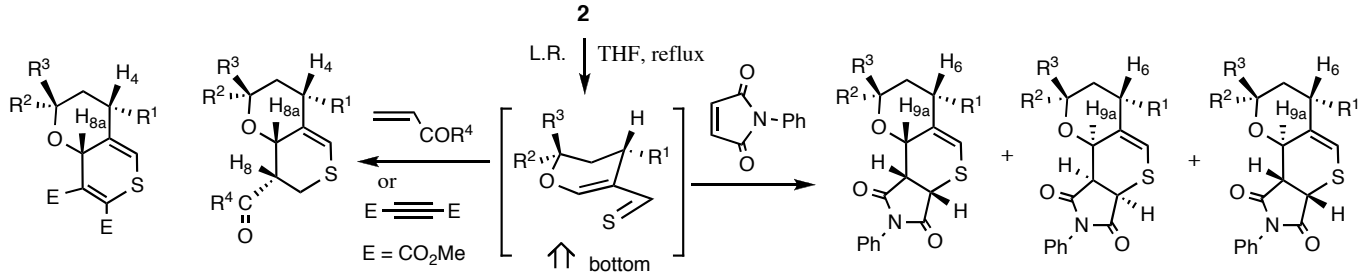
Scheme 1

Similar results were also observed in the reaction of azadiene **3i** with diphenylketene to produce [4 + 2] cycloadducts **5** quantitatively in a *cis:trans* ratio of 72:28 (entry 9). No isomer **5** isomerized under the reaction conditions.

Next, we examined the second DA reaction of 1-thiadienes **6** with several dienophiles. The monoadducts **2** were converted into **6** in the presence of a dienophile (methyl acrylate, methyl vinyl ketone, and *N*-phenylmaleinimide) by slow addition of a 1,2-dichloroethane solution of Lawesson's reagent (L.R.) with gentle refluxing in THF for several hours, providing the bisadducts (**7**, **8**, **9**)[16–18] in fair to good yields (Table 3). The stereochemistry of the major isomer of **7** obtained from the reaction with dimethyl acetylenedicarboxylate (Entry 1) suggests that the dienophile selectively attacks the thiadiene **6** π-facially

(72:28) from the bottom side, as shown in the Scheme. The reactions of **6b**, **c** generated from **2a** and **2′b**, with methyl acrylate and methyl vinyl ketone, respectively, produced the cycloadducts **8a**, **b**, **d** with both high *endo/exo* selectivity (H_8–H_{8a} *cis*) and diastereo π-facial selectivity (H_4–H_{8a} *cis*) (Entries 2, 3, and 5), whereas the reaction of **6d** with methyl acrylate showed high π-facial selectivity but moderate *endo/exo* selectivity (60:40) (Entry 4). In all cases (Entries 1–5) the dienophile attacks from the bottom side of **6** as observed above (for azadiene **3**). In contrast, the reaction of **6b**, **e** with *N*-phenylmaleinimide gave unusual results in terms of the diastereo π-facial selectivity of the reaction. In the reaction of **6e**, isomer **9** was exclusively formed, whereas the reaction of **6b** produced the *endo*-isomer **9′** and *exo*-isomer **9″** in a ratio of 77:23, both of which are likely to be formed arising from the top side-attack of the dienophile onto the diene moiety. A further detailed study will be necessary to explain these observations.

Table 3. Generation and second HDA cycloaddition of thiadienes **6**.



Entry	**2**	R^1	R^2	R^3	R^4	Thiadiene	Adduct	Yield[a] / %	*Endo:exo*[b]	π-Facial[b]
1	**2g**	*p*-Tol	Ph	Ph	–	**6a**	**7**	65	–	72:28
2	**2a**	AcNH	Ph	Ph	MeO	**6b**	**8a**	78	> 95:5	> 95:5
3	**2′b**[c]	AcNH	H	Ph	MeO	**6c**	**8b**	88	> 95:5	> 95:5
4	**2f**	Ph	Ph	Ph	MeO	**6d**	**8c**	78	60:40	> 95:5
5	**2a**	AcNH	Ph	Ph	Me	**6b**	**8d**	60	> 95:5	> 95:5
6	**2a**	AcNH	Ph	Ph	–	**6b**	**9a**	80	77:23[d]	> 95:5[d]
7	**2b**	AcNH	Ph	H	–	**6e**	**9b**	74	> 95:5[e]	> 95:5[e]

[a] Isolated yield. [b] Ratios of stereoisomers determined based on ^{1}H NMR integration. Ratio >95:5 denotes that no minor *trans* isomer was detected. [c] A prime mark in **2′** denotes a *trans* relationship between the R^1 and R^2 groups. [d] **9**:**9′**:**9″** = 0:77:23. [e] **9**:**9′**:**9″** = 100:0:0.

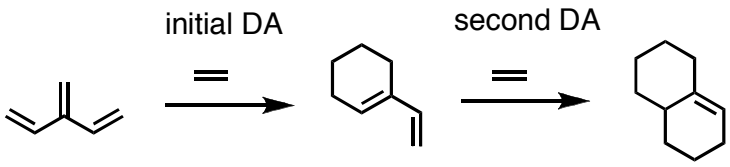
REFERENCES AND NOTES

1. (a) N. Hall, *Science,* 1994, **266**, 32. (b) T.-L. Ho, 'Tandem Organic Reactions,' Wiley, New York, 1992. (c) (for domino reactions) L. F. Tietze, G. Brasche, and K. M. Gericke, 'Domino Reactions in Organic Synthesis,' Wiley-VCH, Weinheim, 2006. (d) L. F. Tietze, *Chem. Rev.,* 1996, **96**, 115. (e) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.,* 1993, **32**, 131. (f) S. E. Denmark and A. Thorarensen, *Chem. Rev.,* 1996, **96**, 137. (g) J. D. Winkler, *Chem. Rev.,* 1996, **96**, 167. (h) I. Ryu, N. Sonoda, and D. P. Curran, *Chem. Rev.,* 1996, **96**, 177. (i) P. J. Parsons, C. S. Penkett, and A. J. Shell,

Chem. Rev., 1996, **96**, 195. (j) (for cascade processes) A. Padwa and M. D. Weingarten, *Chem. Rev.,* 1996, **96**, 223. (k) K. Neuschütz, J. Velker, and R. Neier, *Synthesis,* 1998, 227.

2. (a) D. L. Boger and S. M. Weinreb, 'Hetero Diels-Alder Methodology in Organic Synthesis,' Academic Press, San Diego, 1987. (b) D. L. Boger, 'Comprehensive Organic Synthesis,' ed. by L. A. Paquette, B. M. Trost, and I. Fleming, Pergamon, Oxford, 1991, Vol. 5, p. 451. (c) L. F. Tietze and G. Kettschau, *Top. Curr. Chem.*, 1997, **189**, 1. (d) S. M. Weinreb, *Top. Curr. Chem.*, 1997, **190**, 131. (e) P. Buonora, J.-C. Olsen, and T. Oh, *Tetrahedron*, 2001, **57**, 6099. (f) M. Behforouz and M. Ahmadian, *Tetrahedron*, 2000, **56**, 5259. (g) S. Jayakumar, M. P. S. Ishar, and M. P. Mahajan, *Tetrahedron,* 2002, **58**, 379. (h) K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2000, **39**, 3558 and references cited therein.

3. The DTDA reaction can usually be defined by two sequential DA cycloadditions that involve an initial DA reaction of a cross-conjugated triene (or its equivalents) with a dienophile, followed by a second DA cycloaddition with a dienophile on the newly formed, transmitted diene unit of the monoadduct to give a bisadduct. The diene-transmissive hetero-Diels–Alder (DTHDA) reaction is a special case of the DTDA reaction 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 literatures in reference 4. For DTHDA reactions of heterotrienes, see the literatures in references 5–10.



4. For DT(H)DA of carbotrienes and carbotetraenes: (a) A. T. Blomquist and J. A. Verdol, *J. Am. Chem. Soc.*, 1955, **77**, 81. (b) W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, 1955, **77**, 1133. (c) O. Tsuge, E. Wada, and S. Kanemasa, *Chem. Lett.*, 1983, 239. (d) O. Tsuge, S. Kanemasa, E. Wada, and H. Sakoh, *Yuki Gosei Kagaku Kyokaishi*, 1986, **44**, 756 and references cited therein. (e) O. Tsuge, T. Hatta, K. Yakata, and H. Maeda, *Chem. Lett.*, 1994, 1833. (f) A. Hosomi, T. Masunari, Y. Tominaga, T. Yanagi, and M. Hojo, *Tetrahedron Lett.,* 1990, **31**, 6201. (g) W. Adam, T. Deufel, R. Finzel, A. G. Griesbeck, and J. Hirt, *J. Org. Chem.,* 1992, **57**, 3991. (h) B. Trost and M. Shimizu, *J. Am. Chem. Soc.*, 1982, **104**, 4299. (i) S. Woo, S. Legoupy, S. Parra, and A. G. Fallis, *Org. Lett.*, 1999, **1**, 1013. (j) S. Woo, N. Squire, and A. G. Fallis, *Org. Lett.*, 1999, **1**, 573. (k) M. S. Souweha, A. Arab, M. ApSimon, and A. G. Fallis, *Org. Lett.*, 2007, **9**, 615. (l) M. S. Souweha, F. D. Enright, and A. G. Fallis, *Org. Lett.*, 2007, **9**, 5163. (m) O. Kwon, S. B. Park, and S. L. Schreiber, *J. Am. Chem. Soc.*, 2002, **124**, 13402. (n) A. D. Payne, A. C. Willis, and M. S. Sherburn, *J. Am. Chem. Soc.*, 2005, **127**, 12188. (o) K. M. Brummond and L. You, *Tetrahedron*, 2005, **61**, 6180. (p) B. Mitasev, B. Yan, and K. M. Brummond, *Heterocycles*, 2006, **70**, 367. (q) T. A. Bradford, A. D.

Payne, A. C. Willis, M. N. Paddon-Row, and M. S. Sherburn, *Org. Lett.*, 2007, **9**, 4861.

5. For intermolecular DTHDA of thiatrienes: S. Motoki, Y. Matsuo, and Y. Terauchi, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 284.
6. For intramolecular DTHDA of thiatrienes: T. Saito, H. Kimura, K. Sakamaki, T. Karakasa, and S. Moriyama, *Chem. Commun.*, 1996, 811.
7. (a) O. Tsuge, T. Hatta, H. Yoshitomi, K. Kurosaka, T. Fujiwara, H. Maeda, and A. Kakehi, *Heterocycles*, 1995, **41**, 225. (b) O. Tsuge, T. Hatta, T. Fujiwara, T. Yokohari, A. Tsuge, and T. Moriguchi, *Heterocycles*, 1999, **50**, 661.
8. (a) C. Spino and G. Liu, *J. Org. Chem.*, 1993, **58**, 817. (b) C. Spino and G. Liu, N. Tu, and S. Girard, *J. Org. Chem.*, 1994, **59**, 5596. (c) C. Spino, B. Hill, P. Dubé, and S. Gingras, *Can. J. Chem.*, 2003, **81**, 81. (d) A. Dion, P. Dubé, and C. Spino, *Org. Lett.*, 2005, **7**, 5601. (e) C. Spino, *Synlett* 2006, 23. (f) S. Perreault and C. Spino, *Org. Lett.*, 2006, **8**, 4385.
9. T. Saito, H. Kimura, T. Chonan, T. Soda, and T. Karakasa, *Chem. Commun.*, 1997, 1013.
10. T. Saito, S. Kobayashi, M. Ohgaki, M. Wada, and C. Nagahiro, *Tetrahedron Lett.*, 2002, **43**, 2627.
11. 2-(Acetylaminomethylene)propanedial (**1a**) was prepared by the reaction of triformylmethane with acetamide in the presence of BF_3•OEt_2. Z. Arnold, M. Budêsínský, and P. Fielder, *Synthesis*, 1989, 858. Z. Arnold, M. Budêsínský, and M. Pankova, *Coll. Czech. Chem. Commun.*, 1991, **56**, 1019.
12. ***N*-(5-Formyl-2,2-diphenyl-3,4-dihydro-2*H*-pyran-4-yl)acetamide (2a):** Colorless crystals; mp 173–175 °C; IR (KBr) ν_{max} 3255, 1820, 1681, 1635 cm^{-1}; ^{1}H-NMR (300 MHz/$CDCl_3$); δ 1.69 (s, 3H, Ac), 2.83 (dd, 1H, J = 5.7, 14.5 Hz, H-3'), 3.02 (dd, 1H, J = 5.2, 14.5 Hz, H-3), 4.75 (ddd, 1H, J = 5.2, 5.7, 5.7 Hz, H-4), 5.29 (d, 1H, J = 5.7 Hz, NH), 7.21–7.38 (m, 8H, Ar), 7.40–7.48 (m, 2H, Ar), 7.67 (s, 1H, H-6), 9.26 (s, 1H, CHO); ^{13}C-NMR (75.5 MHz/$CDCl_3$) δ 22.87 (CH_3), 36.46 (CH_2), 38.83 (CH), 85.61 (C), 118.21 (C), 125.29 (CH×2), 125.55 (CH×2), 127.60 (CH), 128.00 (CH), 128.32 (CH×2), 128.54 (CH×2), 141.97 (C), 142.14 (C), 165.37 (CH), 169.78 (C), 189.03 (CH); Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.70; H, 5.96; N, 4.36. Found: C, 74.39; H, 6.09; N, 4.45.
13. (Acyloxymethylene)propanedials (**1b**, **c**) were prepared by the reaction of triformylmethane with acyl anhydride in the presence of a small amount of pyridine.
14. 2-(Arylmethylene)propanedials (**1d**, **e**) were prepared according to the known method: (a) Z. Arnold, V. Král, and D. Dvorak, *Tetrahedron Lett.*, 1982, **23**, 1725. (b) D. Dvorak, D. Saman, Z. Arnold, I. Císarova, and V. Petricek, *Coll. Czech. Chem. Commun.*, 1992, **57**, 2337. Cycloaddition reactions of **1d** and its aryl-substituted analogues with electron-rich dienophiles such as ethyl vinyl ether have also been reported.
15. ***N*-[7-Ethoxy-3-(4-methoxyphenyl)-2-oxo-1-(toluene-4-sulfonyl)-1,3,5,6,7,8a-hexahydro-2*H*-pyrano[2,3-*d*]pyrimidin-5-yl]-acetamide (4a):** Yellowish crystals; mp 101–103 °C; IR (KBr) ν_{max}

3412, 1682 cm^{-1}; ^{1}H-NMR (500 MHz/$CDCl_3$) δ 1.37 (t, 3H, J = 7.0 Hz, Me (OEt)), 1.99 (br ddd, 1H, J = 0.9, 2.0, 14.2 Hz, H-2), 2.04 (s, 3H, Ac), 2.19 (ddd, 1H, J = 4.1, 5.2, 14.2 Hz, H-3), 2.39 (s, 3H, Me (Ts)), 3.68 (dq, 1H, J = 7.0, 9.3 Hz, CH_2 (OEt)), 3.75 (s, 3H, OMe), 4.38 (dq, 1H, J = 7.0, 9.3 Hz, CH_2 (OEt)), 4.71 (br ddd, 1H, J = 2.0, 5.2, 7.5 Hz, H-4), 5.15 (br dd, 1H, J = 0.9, 4.1 Hz, H-1), 6.37 (s, 1H, H-6), 6.70 (s, 1H, H-5), 6.82 (d, 2H, J = 9.0 Hz, Ar), 7.10 (d, 2H, J = 9.0 Hz, Ar), 7.14 (br d, 1H, J = 7.5 Hz, NH), 7.27 (d, 2H, J = 8.4 Hz, Ar), 8.00 (d, 2H, J = 8.4 Hz, Ar); ^{13}C-NMR (126 MHz/$CDCl_3$) δ 14.97 (CH_3), 21.51 (CH_3), 23.52 (CH_3), 37.53 (CH_2), 46.22 (CH), 55.36 (CH_3), 64.07 (CH_2), 74.30 (CH), 98.90 (CH), 109.99 (C), 114.27 (CH×2), 124.71 (CH), 127.69 (CH×2), 129.09 (CH×2), 129.14 (CH×2), 131.77 (C), 136.38 (C), 144.38 (C), 147.49 (C), 158.85 (C), 169.27 (C).

16. **Dimethyl 2,2-diphenyl-4-*p*-tolyl-2,3,4,8a-tetrahydrothiopyrano[4,3-*b*]pyran-7,8-dicarboxylate (7)** (*cis* isomer): Colorless crystals; mp 172–173 °C; IR (KBr) ν_{max} 1726 cm^{-1}; ^{1}H-NMR (400 MHz/$CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.54 (dd, 1H, J = 13.7, 13.7 Hz, H-3), 3.04 (dd, 1H, J = 3.4, 13.7 Hz, H-3'), 3.81 (br d, 1H, J = 13.7 Hz, H-4), 3.82 (s, 3H, OMe), 3.92 (s, 3H, OMe), 5.28 (s, 1H, H-8a), 5.57 (s, 1H, H-5), 7.10–7.50 (m, 14H, Ar); ^{13}C-NMR (100 MHz/$CDCl_3$) δ 21.03 (CH_3), 43.85 (CH_2), 45.29 (CH), 52.35 (CH_3), 53.18 (CH_3), 67.65 (CH), 81.70 (C), 110.55 (CH), 124.55 (CH×2), 126.51 (CH), 127.45 (CH), 127.49 (CH), 127.70 (CH), 128.07 (CH×2), 128.57 (CH), 128.78 (CH×2), 129.69 (C), 133.78 (C), 135.96 (C), 137.17 (C), 141.43 (C), 147.64 (C), 163.73 (C); EIMS (*m*/*z*) 512 (M^+, 4).

17. **4-Acetylamino-2,2-diphenyl-3,4,8,8a-tetrahydro-2*H*,7*H*-thiopyrano[4,3-*b*]pyran-8-carboxylic acid methyl ester (8a):** Colorless crystals; mp 236–238 °C; IR (KBr) ν_{max} 3247, 1812, 1735, 1643 cm^{-1}; ^{1}H-NMR (300 MHz/$CDCl_3$) δ 1.78 (dd, 1H, J = 12.7, 13.3 Hz, H-3'), 2.06 (s, 3H, Ac), 2.86–2.99 (m, 2H, H-8 & H-7), 3.06 (dd, 1H, J = 4.0, 13.3 Hz, H-3), 3.22 (dd, 1H, J = 3.3, 13.1 Hz, H-7'), 3.79 (s, 3H, MeO), 4.25 (d, 1H, J = 4.4 Hz, H-8a), 5.01 (ddd, 1H, J = 4.0, 8.4, 12.7 Hz, H-4), 5.43 (d, 1H, J = 8.4 Hz, NH), 6.01 (s, 1H, H-5), 7.07–7.19 (m, 2H, Ar), 7.19–7.32 (m, 4H, Ar), 7.34–7.46 (m, 4H, Ar); ^{13}C-NMR (75.5 MHz/$CDCl_3$) δ 23.26 (CH_2), 23.37 (CH_3), 45.27 (CH_2), 46.47 (CH), 49.28 (CH), 51.70 (CH_3), 65.70 (CH), 81.22 (C), 113.14 (CH), 124.64 (CH×2), 126.60 (CH), 127.66 (CH×2), 128.01 (CH×2), 128.46 (CH), 128.85 (CH×2), 132.08 (C), 141.68 (C), 147.39 (C), 169.47 (C), 171.55 (C); Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 67.85; H, 6.08; N, 3.27.

18. ***N*-(1,3-Dioxo-2,8-diphenyl-1,2,3,3a,7,8,9a,9b-octahydro-6*H*-9-oxa-4-thia-2-aza-cyclopenta[*a*]-naphthalen-6-yl)acetamide (9b):** Colorless crystals; mp 112–114 °C; IR (KBr) ν_{max} 3262, 1781, 1712, 1658 cm^{-1}; ^{1}H-NMR (600 MHz/$CDCl_3$) δ 1.77 (ddd, 1H, J = 11.1, 11.3, 12.8 Hz, H-7'), 2.05 (s, 3H, Ac), 2.28 (ddd, 1H, J = 2.6, 5.3, 12.8 Hz, H-7), 4.02 (dd, 1H, J = 4.6, 9.4 Hz, H-9b), 4.08 (d,

1H, *J* = 1.2, 9.4 Hz, H-3a), 4.87 (dd, 1H, *J* = 2.3, 4.6 Hz, H-9a), 5.08 (dddd, 1H, *J* = 2.3, 5.5, 8.8, 11.3 Hz, H-6), 5.49 (d, 1H, *J* = 8.8 Hz, NH), 5.58 (dd, 1H, *J* = 2.6, 11.1 Hz, H-8), 6.33 (d, 1H, *J* = 1.2 Hz, H-5), 7.27–7.33 (m, 3H, Ar), 7.37 (dd, 2H, *J* = 7.7, 7.7 Hz, Ar), 7.39–7.43 (m, 3H, Ar), 7.49 (dd, 2H, *J* = 7.8, 7.8 Hz, Ar); ^{13}C-NMR (150 MHz/$CDCl_3$) δ 23.27 (CH_3), 37.62 (CH_2), 43.47 (CH), 47.76 (CH), 51.19 (CH), 74.57 (CH), 75.00 (CH), 115.36 (CH), 126.12 (CH×2), 126.66 (CH×2), 127.99 (CH), 128.56 (CH×2), 129.03 (CH), 131.35 (C), 141.33 (C), 141.45 (C), 169.67 (C), 174.09 (C), 174.52 (C); HRMS (ESI): Calcd for $C_{24}H_{22}N_2NaO_4S$: $[M+Na]^+$ 457.1199, Found: 457.1207.