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Synthesis of jadomycin A and related jadomycin aglycons: structural re-examination of jadomycins S and T may be needed

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ABSTRACT

Jadomycin A and related jadomycin M and W aglycons were synthesized. Easy re-construction of 4-(hydroxymethyl)-1,3-oxazolidin-5-one system into an isomeric 1,3-oxazolidine-4-carboxylic acid system during the synthetic trial of jadomycin S aglycon requests us to more precisely re-examine the structures proposed for jadomycins S and T, derived from hydroxyl-containing amino acids of L-serine and L-threonine, respectively.

Jadomycin antibiotics have a unique 8*H*-benzo[*b*]oxazolo[3,2-*f*]phenanthridine skeleton incorporating an amino acid unit in the 1,3-oxazolidin-5-one ring[1–4] and biogenetically derived from the same precursor that gilvocarcins.[5] The L-isoleucine-containing analogs, jadomycins A (**1**) and B (**2**), were firstly isolated from *Streptomyces venezuelae* in 1991.[1–3] After then a range of jadomycin B (**2**) congeners carrying L-digitoxose at the 12-phenolic function has been artificially produced by addition of the corresponding amino acid component to culture medium during cultivation and interesting biological activities such as anti-MRSA,[6] DNA cleaving,[7] and cytotoxic activities[6] were found in jadomycins B (**2**), L (L-leucine), S (L-serine), and T (L-threonine).

In the previous Letter,[8] we reported the synthesis of dimethyljadomycin A (**3**) through spirolactonyltetralone as a synthetic intermediate based on our arnottin II synthesis;[9] however, this approach could not be applied to the synthesis of natural jadomycin A (**1**) itself because of resistant demethylation. Therefore, we further approached to the development of synthetic method applicable to diverse jadomycin analogs by improving our previous method. In this communication we report the syntheses of jadomycin A (**1**) and related jadomycins M **4** and W **5** aglycons. In addition, we would like to propose to re-examine the 4-(hydroxymethyl)-1,3-oxazolidin-5-one system in jadomycins S and T, derived from hydroxy-containing amino acids of L-serine and L-threonine, respectively, because of its easy re-construction to an isomeric 1,3-oxazolidin-4-carboxylic acid system during the synthetic trials of jadomycin S aglycon **6**.

In the synthesis of dimethyljadomycin A (**3**), spontaneous isoquinoline–oxazolidone cyclization was successfully applied to the final construction of jadomycin skeleton by oxidation of the benzyl alcohol unit on the aryl pendant of 2-aryl-1,4-naphthoquinone core carrying amino acid function located at the adjacent position of the aryl group.[8] Thus, we decided the use of the same cyclization procedure in the synthesis of jadomycin A (**1**) and related jadomycin aglycons. Retrosynthetic analysis is shown in Scheme 1, in which a methoxymethyl (MOM)-protected 2-[2-(hydroxymethyl)aryl]-1,4-naphthoquinone **8** was designed as a common synthetic intermediate for jadomycin aglycons.

The coupling partners, benzoxaborole **9**[10] and bromojuglone **10**,[11] were prepared from commercially available 3,5-dimethylphenol and 1,5-dihydroxynaphthalene in 27% and 59% yields, respectively, through each four steps. Suzuki–Miyaura cross-coupling reaction of **9** and **10** was optimized by the use of $PdCl_2$(dppf) as palladium catalyst and CsF as base[12] in aqueous THF (THF/H_2O = 10:1) at room temperature for 28 h. Thus, a common 2-[2-(hydroxymethyl)aryl]-1,4-naphthoquinone **8** was provided in an 87% yield as a ca 2:1 mixture of atropisomers. Treatment of 2-aryl-1,4-naphthoquinone **8** with L-isoleucine in aqueous ethanol in the presence of triethylamine gave amino acid-inserted naphthoquinone **11** in a 56% yield by Michael addition–air oxidation reactions.[13] Oxidation of **11** with Dess–Martin periodinane (DMP) afforded the MOM-protected jadomycin A **12**. Removal of protecting group in **12** with 4 N HCl smoothly yielded jadomycin A[14] (**1**) as a diastereomeric mixture of the 3a*S*- and 3a*R*-isomers at the ratio of ca 5:1[15] (Scheme 2). Jadomycin M aglycon **4** was similarly synthesized from **8** using L-methionine as an amino acid component.

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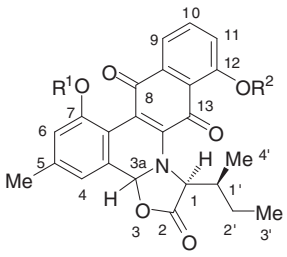
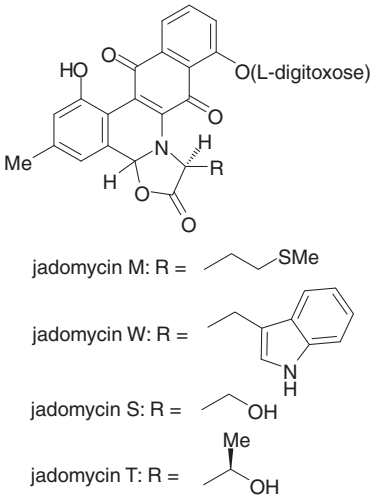


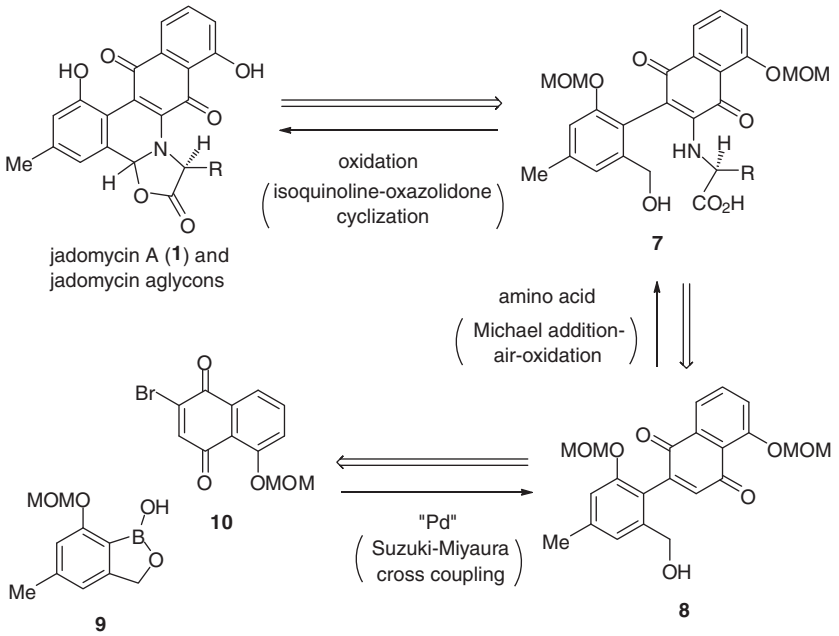
jadomycin A (**1**: $R^1 = R^2 = H$)
jadomycin B (**2**: $R^1 = H$; R^2 = L-digitoxose)
dimethyljadomycin A (**3**: $R^1 = R^2 = Me$)



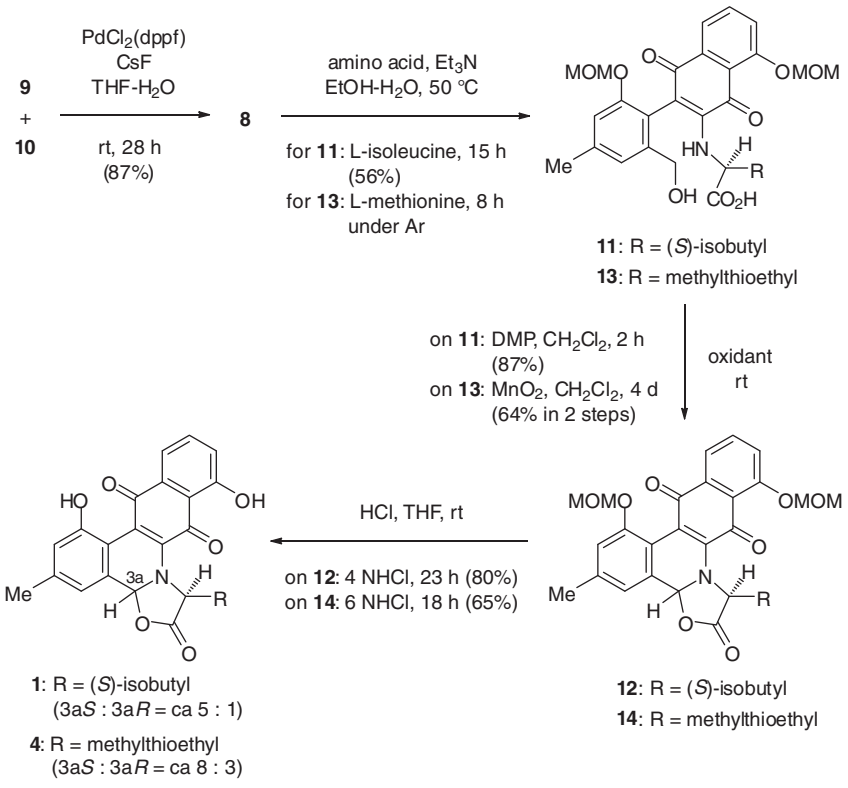
In this reaction sequence, changes of reaction conditions were requested; the reaction under anaerobic condition in the introduction of the amino acid unit and the use of manganese oxide in place of DMP in the second oxidation step for isoquinoline–oxazolidone cyclization due to possible oxidation of the sulfide function in the methionine unit (Scheme 2).

Next, we targeted jadomycin W aglycon **5** carrying L-tryptophan as an amino acid unit (Scheme 3). L-Tryptophan was successfully introduced to the naphthoquinone core **8**; however, the following oxidative cyclization disappointed us. Replacement of L-tryptophan by its *N*-Boc-protected derivative gave an intended jadomycin skeleton **17** in a 66% yield in two steps. Although only a complex mixture was formed in trials for the removal of protecting group under various conditions including with routinely used HCl, a combination of TMSOTf and 2,6-lutidine in the presence of *p*-thiocresol[16] afforded jadomycin W aglycon **5** in a 54% yield as an inseparable mixture containing a major 3a*S*-isomer.

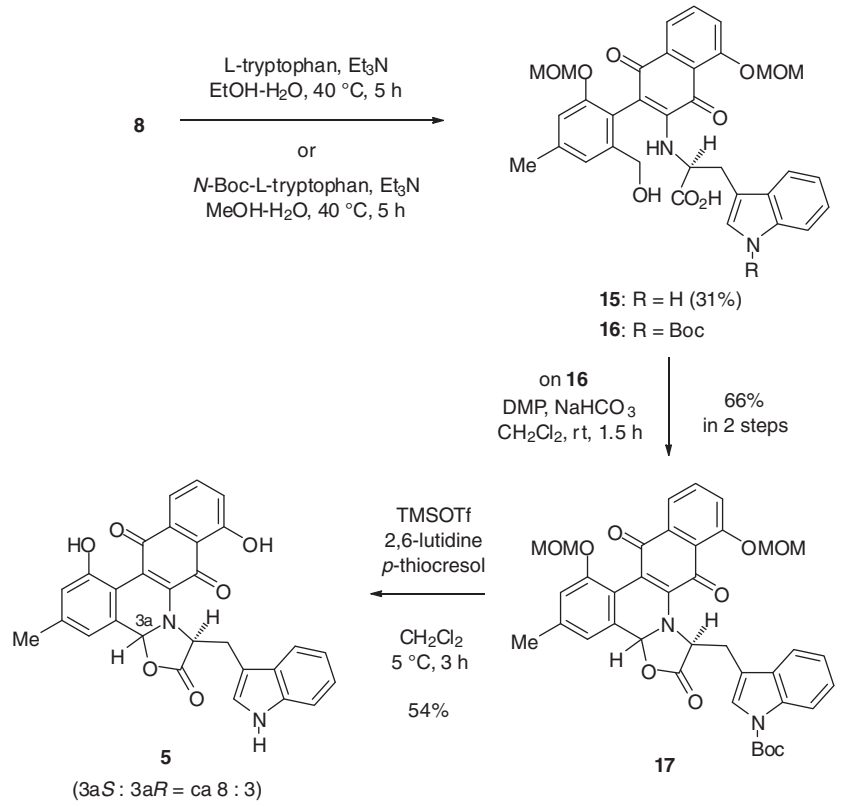
Finally, the synthesis of jadomycin S aglycon **6** derived from L-serine was attempted (Scheme 4). Treatment of the naphthoquinone **8** with L-serine afforded an amino acid-inserted product **18** in a 56% yield; however, the following oxidative cyclization failed, similar to the use of unprotected tryptophan as shown in Scheme 3. Protection of the hydroxy group as *tert*-butyl ether gave a jadomycin skeleton **21** in high two steps yield from **8**, but only a complex mixture was formed in the next deprotection trials. On the other hand, when TBS-protection was applied, expected deprotection in jadomycin skeleton **22** was suggested by disappearance of both MOM and TBS functions in the ^{1}H NMR spectrum of a crude



Scheme 1.



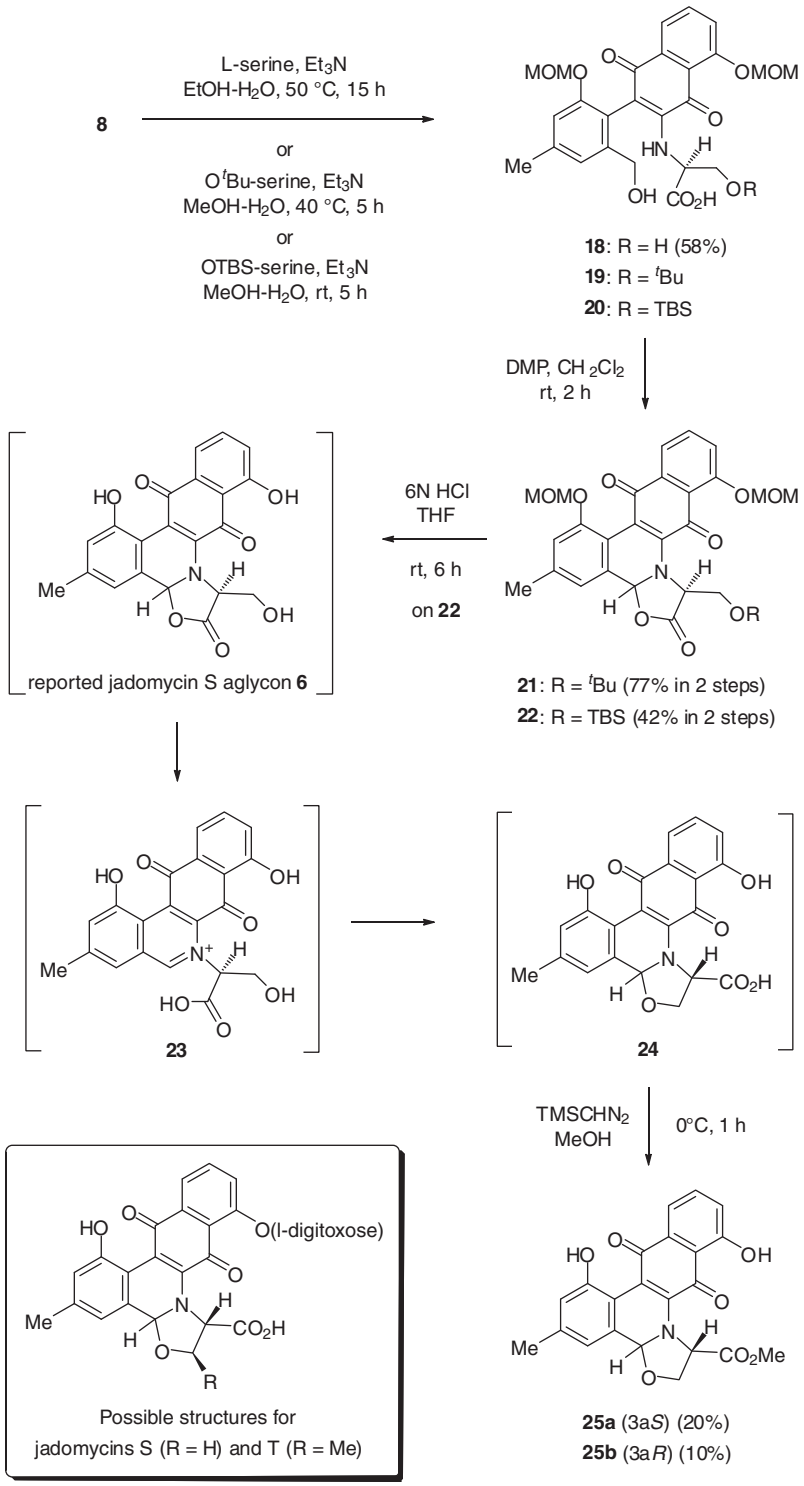
Scheme 2.



Scheme 3.

reaction product **24**, in spite of unsuccessful isolation of the product as a pure form due to its instability.

The 1,3-oxazolidin-5-one system in jadomycin skeletons, as expected, shows a characteristic carbonyl absorption at around



Scheme 4.

1800 cm^{-1} in the IR spectrum [e.g. 1806 cm^{-1} for jadomycin B (**2**) and 1804 cm^{-1} for jadomycin F (L-phenylalanine)[17]] (entries 1 and 5, Table 1). In fact, a carbonyl absorption at 1807 cm^{-1}, in addition to 1664 cm^{-1} due to quinone carbonyl absorption, was detected in the isoquinoline–oxazolidone cyclization product **22** as well as our synthesized related compounds (e.g. entries 10–12, Table 1), while two carbonyl absorptions at 1717 and 1637 cm^{-1} were observed in a crude deprotected product **24**. These facts indicated that 4-(hydroxymethyl)-1,3-oxazolidin-5-one system in a jadomycin skeleton **22** was re-constructed to 1,3-oxazolidine-4-carboxylic acid system in **24** through a ring-opened isoquinolinium salt **23**, in which a more nucleophilic hydroxy group than carboxyl one was generated. This speculation was confirmed by the conversion of a crude deprotection product **24** to methyl ester derivative **25** for characterization. Treatment of **24** with trimethylsilyldiazomethane gave two isolable products **25a** and **25b**, showing carbonyl absorptions at 1736 and 1748 cm^{-1} due to an ester function in the IR spectra (entries 13 and 14, Table 1), in 20% and 10% yields,

Table 1
Carbonyl absorptions in the IR and chemical shifts assignable to the C3a–H signals in the NMR spectra of jadomycins in literatures[6,17] and aglycons prepared[a]

Entry	Compounds	ν_{max}cm^{-1}	δ_H	δ_C
Jadomycins				
1.	B (L-isoleucine) (**2**)[17]	1806	6.31 (3a*S*)	88.1
			6.72 (3a*R*)	88.5
2.	V (L-valine)[17]	n.d.[b]	6.30 (3a*S*)	n.d.[b]
			6.77 (3a*R*)	n.d.[b]
3.	ALA (L-alanine)[17]	n.d.[b]	6.39 (3a*S*)	88.3
			6.80 (3a*R*)	87.1
4.	M (L-methionine)[6]	n.d.[b]	6.20 (3a*S*)	87.5
			6.50 (3a*R*)	87.4
5.	F (L-phenylalanine)[17]	1804	6.08 (3a*S*)	88.0
			5.93(3a*R*)	87.9
6.	Y (L-tyrosine)[6]	n.d.[b]	5.92 (3a*S*)	87.2
			5.25 (3a*R*)	87.8
7.	W (L-tryptophan)[6]	n.d.[b]	5.96 (3a*S*)	n.d.[b]
			5.11 (3a*R*)	n.d.[b]
8.	S (L-serine)[17]	1685	5.84 (3a*R*)	89.8
9.	T (L-threonine)[17]	1690	5.87 (3a*R*)	89.4
Aglycons				
10.	B (**1**)	1808	6.17 (major)	87.1
			6.54 (minor)	88.1
11.	M (**4**)	1801	6.19 (major)	87.3
			6.62 (minor)	87.4
12.	W (**5**)	1804	5.90 (major)	87.1
			5.28 (minor)	88.0
13.	Ester **25a**	1736	5.96 (3a*S*)	89.0
14.	Ester **25b**	1748	5.85 (3a*R*)	89.4

[a] The NMR and the IR data of jadomycins were measured in acetone-d_6 and with KBr, respectively, in Ref. 17, but no description in Ref. 6. On jadomycin A (**1**), aglycons M **4** and W **5**, and esters **25a** and **25b** prepared by us $CDCl_3$ and ATR were used in the NMR and the IR measurement, respectively.
[b] No data cited.

respectively. Precise examination of them using NMR spectra (NOE, HMQC, HMBC) allowed us to deduce a major isomer **25a** to be methyl 1,3-oxazolidine-4-carboxylate with 3a*S* stereochemistry.

It has been reported that jadomycins S and T incorporating a hydroxy-containing amino acid show a carbonyl absorption at 1685 cm^{-1} and 1690 cm^{-1}, respectively, but not at around 1800 cm^{-1}, in their IR spectra[17] (entries 8 and 9, Table 1). Strong hydrogen bond between the side chain hydroxy and the C13-carbonyl group, locking the oxazolidone ring into place, is proposed for them based on molecular modeling experiments;[17] however, it may be difficult to clearly explain the lack of a characteristic absorption at around 1800 cm^{-1} for an oxazolidone system in the IR spectra even if the ring is fixed.

Chemical shifts assignable to the C3a-H signals of natural jadomycins in the NMR spectra in literature[6,17] and aglycons prepared here are also summarized in Table 1. In the latter aglycons, esters **25a** and **25b** carrying a 1,3-oxazolidine-4-carboxylic acid system (entries 13 and 14) showed slightly lower-field shifted signals in the ^{13}C NMR spectra compared to other aglycons carrying a 1,3-oxazolidin-5-one system (entries 10–12), and showed slightly higher-field shifted signals in the ^{1}H NMR spectra compared to other aglycons except an aglycon carrying an aromatic side chain such as a tryptophan-inserted aglycon W **5** (entry 12).[18] In the former jadomycin series, the same tendency[19] was observed in jadomycins S and T (entries 8 and 9), possibly suggesting that these hydroxy-containing amino acid-derived jadomycins have 1,3-oxazolidine-4-carboxylic acid, but not 1,3-oxazolidin-5-one, system.

Furthermore, in jadomycin N (L-aspargine) a pyrimidone system, not an oxazolidone one, resulting from more preferential cyclization by the amide than the carboxylic acid functions, has been formed.[6,17] Although no positive results have been obtained in the feeding experiment of L-threonine methyl ester by *S. venezuelae* ISP 5230, anticipating that hydroxy functionality would potentially cyclize with aldimine intermediate like **23** to form an oxazolidine ring,[4] our observation of ring re-construction of oxazolidone to oxazolidine, albeit under non-physiological conditions, could claim that the 4-(hydroxymethyl)-1,3-oxazolidin-5-one ring system proposed for hydroxy-containing amino acid-derived jadomycins may be more precisely re-examined.

In conclusion, jadomycin A and related jadomycin aglycons were synthesized from a common 2-aryl-1,4-naphthoquinone precursor by introducing an appropriate amino acid unit. Our synthetic method could be applicable to the synthesis of other jadomycin aglycons containing a different amino acid unit. In addition, we observed easy re-construction of 4-(hydroxymethyl)-1,3-oxazolidin-5-one system to 1,3-oxazolidine-4-carboxylic acid one in the synthetic trial of jadomycin S aglycon, suggesting the possibility to revise the 4-(hydroxymethyl)-1,3-oxazolidin-5-one system in jadomycins S (or DS from D-serine) and T (or DT from D-threonine) incorporating a hydroxy-containing amino acid to an isomeric 1,3-oxazolidine-4-carboxylic acid system. At present further synthetic approaches to natural jadomycin antibiotics carrying L-digitoxose as a sugar unit is under investigation in our laboratory.

Supplementary data

Supplementary data (experimental procedures and spectral data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.160.

References and notes

1. Ayer, S. W.; McInnes, A. G.; Thibault, P.; Walter, J. A.; Doull, J. L.; Parnell, T.; Vining, L. C. *Tetrahedron Lett.* **1991**, *32*, 6301–6304.
2. Doull, J. L.; Ayer, S. W.; Singh, A. K.; Thibault, P. *J. Antibiotics* **1993**, *46*, 869–871.
3. Doull, J. L.; Singh, A. K.; Hoare, M.; Ayer, S. W. *J. Ind. Microbiol.* **1994**, *13*, 120–125.
4. Syvitski, R. T.; Borissow, C. N.; Graham, C. L.; Jakeman, D. L. *Org. Lett.* **2006**, *8*, 697–700.
5. Kharel, M. K.; Zhu, L.; Liu, T.; Rohr, J. *J. Am. Chem. Soc.* **2007**, *129*, 3780–3781.
6. Borissou, C. N.; Graham, C. L.; Syvitski, R. T.; Reid, T. R.; Blay, J.; Jakeman, D. L. *Chem. Biol. Chem.* **2007**, *8*, 1198–1203.
7. Cottreaw, K. M.; Spencer, C.; Wentzell, J. R.; Graham, C. L.; Borissou, C. N.; Jakeman, D. L.; McFarland, S. A. *Org. Lett.* **2010**, *12*, 1172–1175.
8. Akagi, Y.; Yamada, S.-I.; Etomi, N.; Kumamto, T.; Nakanishi, W.; Ishikawa, T. *Tetrahedron Lett.* **2010**, *51*, 1338–1340.
9. Konno, F.; Ishikwa, T.; Kawahata, M.; Yamaguchi, K. *J. Org. Chem.* **2006**, *71*, 9818–9823.
10. The protocol for the preparation of **9**: Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072–7073.
11. Lei, X.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791.
12. Wright, S. M.; Hageman, D. L.; MacClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097.
13. (a) Shrestha-Dawadi, P. B.; Bittner, S.; Fridkin, M.; Rahimipour, S. *Synthesis* **1996**, 1468–1472; (b) Katrizky, A. R.; Huang, L.; Sakhuja, R. *Synthesis* **2010**, 2011–2016.
14. Shan, M.; Sharif, E. V.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9492–9495.
15. A natural jadomycin A (**1**) had been isolated as a ca 10: 1 diastereomeric mixture of the 3a*S*- and 3a*R*-isomers (see, Ref. 4).
16. Rapid and selective MOM-deprotection using a combination of $ZnBr_2$ and propanethiol had been reported by Ryu et al (*Tetrahedron Lett*. **2010**, *66*, 1673–1677). Lower yields were obtained in the deprotection reactions either without *p*-thiocresol (27%) or in the use of alternative additives (anisole: 24%, AcONa: 31%).
17. Rix, U.; Zheng, J.; Remsing Rix, L. L.; Greenwell, L.; Yang, K.; Rohr, J. *J. Am. Chem. Soc.* **2004**, *126*, 4496–4497.
18. The presence of an aromatic ring in the C1-side chain of jadomycin skeletons could cause anisotropic effect of the C3a–H signal in the ^{1}H NMR spectra.
19. Jadomycins F, Y, and W (entries 5–7) are corresponding to the exceptional cases of aromatic side chain-containing jadomycins in the ^{1}H NMR spectra.