Journal of Molecular Catalysis B: Enzymatic 64 (2010) 113–117

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

journal homepage: www.elsevier.com/locate/molcatb

Bacillus stearothermophilus acetylacetoin synthase: A new catalyst for C–C bond formation

Pier Paolo Giovannini[a,*], Paola Pedrini[a], Valentina Venturi[a], Giancarlo Fantin[b], Alessandro Medici[a]

[a] *Dipartimento di Biologia ed Evoluzione, Università di Ferrara, C.so Ercole I d'Este 32, I-44100 Ferrara, Italy*
[b] *Dipartimento di Chimica, Università di Ferrara, via L. Borsari, I-44100 Ferrara, Italy*

ARTICLE INFO

Article history:
Received 25 November 2009
Received in revised form 23 February 2010
Accepted 2 March 2010
Available online 6 March 2010

Keywords:
Acetylacetoin synthase
Bacillus stearothermophilus
C–C bond formation
Enzyme catalysis
α-Hydroxy-1,3-diketones

ABSTRACT

The synthesis of α-hydroxy-1,3-diketones **2** and **3** from the corresponding 1,2-diketones with *Bacillus stearothermophilus* ATCC2027 acetylacetoin synthase (AAS) was described. The enzyme catalyzed the condensation of the dialkyl- or alkyl-aryl-1,2-diketones **1** with the elimination of a carboxylic acid moiety. The reactions were carried out using either one diketone both acting as donor and acceptor (homo-coupling) or with two different reacting species (cross-coupling). The homo-coupling reactions of the asymmetric dialkyl-1,2-diketones **1c**–**d** afforded a mixture of the regioisomers **2** (30–42%, ee 67–70%) and **3** (19–25%), while only the 1,3-diketones **2a** (57%), **2b** (60%), and **2e** (45%, ee 76%) were obtained using 2,3-butanedione **1a**, 3,4-hexanedione **1b**, and 1-phenyl-1,2-propanedione **1e**, respectively. The cross-coupling reactions of the diketones **1a** and **1b**, and **1b** and **1e** were carried out using various ratios of the donor and the acceptor. In both cases the only cross-coupling product was 3-ethyl-3-hydroxy-2,4-hexanedione **4** (62%, ee 91%).

1. Introduction

C–C bond forming reaction is one of the main goals in synthetic organic chemistry and represents the critical step of many syntheses. In this field the enzymatic C–C bond forming reactions are very attractive for the high chemo-, regio- and enantioselectivity. Nature supplies versatile enzymes that catalyze these reactions under mild conditions (i.e. lyase, transketolase, aldolase) [1,2]. Biocatalytic approaches to carboligation are frequently based on thiamine diphosphate-dependent (ThDP-dependent) enzymes. Benzaldehyde lyase (BAL), benzoyl-formate decarboxylase (BFD), and pyruvate decarboxylase (PDC) are successfully used for both the asymmetric carboligation of two aromatic aldehydes and the cross-carboligation of an aromatic and an aliphatic aldehyde to afford enantiomerically pure α-hydroxy ketones [1,2]. Recently PDC- and BAL-mediated benzoin-type condensation of aliphatic aldehydes has been reported [3]. All these enzymes use ThDP as cofactor to obtain the umpolung of an aldehyde (donor). The new C–C bond is stereoselectively formed by the attack of this carbonyl carbanion on a second aldehyde (acceptor) (Scheme 1).

An interesting ThDP-dependent enzyme is acetylacetoin synthase (AAS) that seems to play a key role in the synthesis of 2,3-butanediol by fermentation with various bacteria [4–8]. The different isomeric forms of butanediol are produced by a catabolic pathway starting from pyruvate and involving various acetoin reductases [9] or by the "butanediol cycle" which existence was reported in different bacteria [10]. In this cycle [11] AAS catalyzes the condensation between two molecules of 2,3-butanedione **1a** (diacetyl) leading to the formation of 3-hydroxy-3-methyl-2,4-pentanedione **2a** (acetylacetoin) and acetic acid [10] (Scheme 2). While with other ThDP-dependent enzymes (i.e. PDC, TK) the leaving groups are carbon dioxide or D-glyceraldehyde-3-phosphate [1,2], with AAS the mechanism is quite different. In this case, the intermediate, obtained by the attack of the AAS-bound ThDP anion on the carbonyl group, undergoes hydrolysis leading to hydroxyethyl-ThDP and acetic acid. The carbanion intermediate attacks a second molecule of diacetyl forming the new C–C bond, and finally, a shift of the alcolate anion allows the release of acetylacetoin and ThDP in hylide form.

Till today very few data have been reported on the purification and characterization of this enzyme [12] and moreover it has never been employed for synthetic purposes.

In the present work *Bacillus stearothermophilus* acetylacetoin synthase has been used in the homo-coupling reactions of the 1,2-diketones **1** to obtain the regioisomeric α-hydroxy-1,3-diketones **2** and **3** (Table 1) and in the cross-coupling reactions of the 1,2-diketones **1a** and **1b**, and **1b** and **1e**, respectively.

* Corresponding author. Tel.: +39 0532 293776; fax: +39 0532 208561.
E-mail address: gvnppl@unife.it (P.P. Giovannini).

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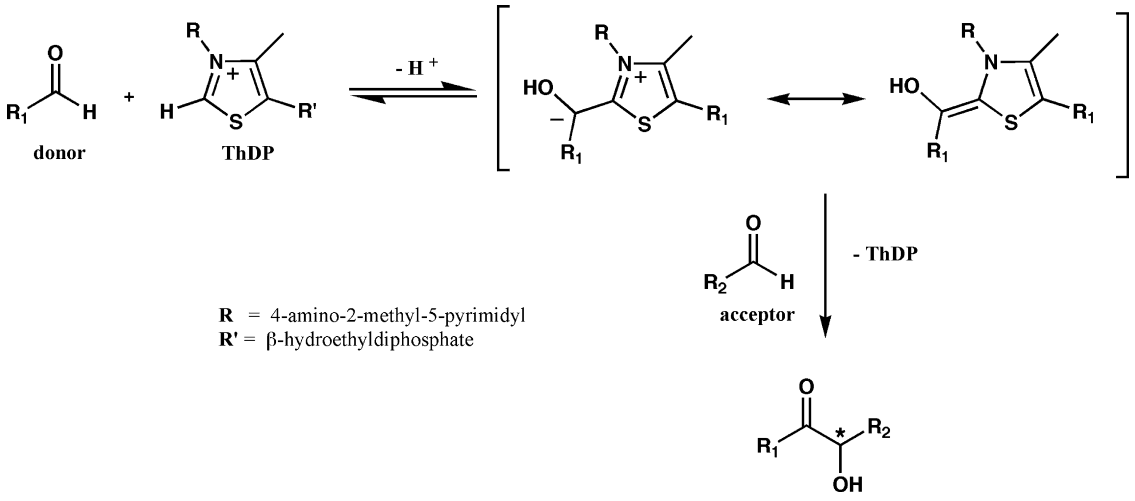
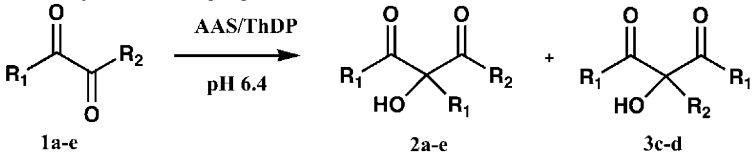
doi:10.1016/j.molcatb.2010.03.001



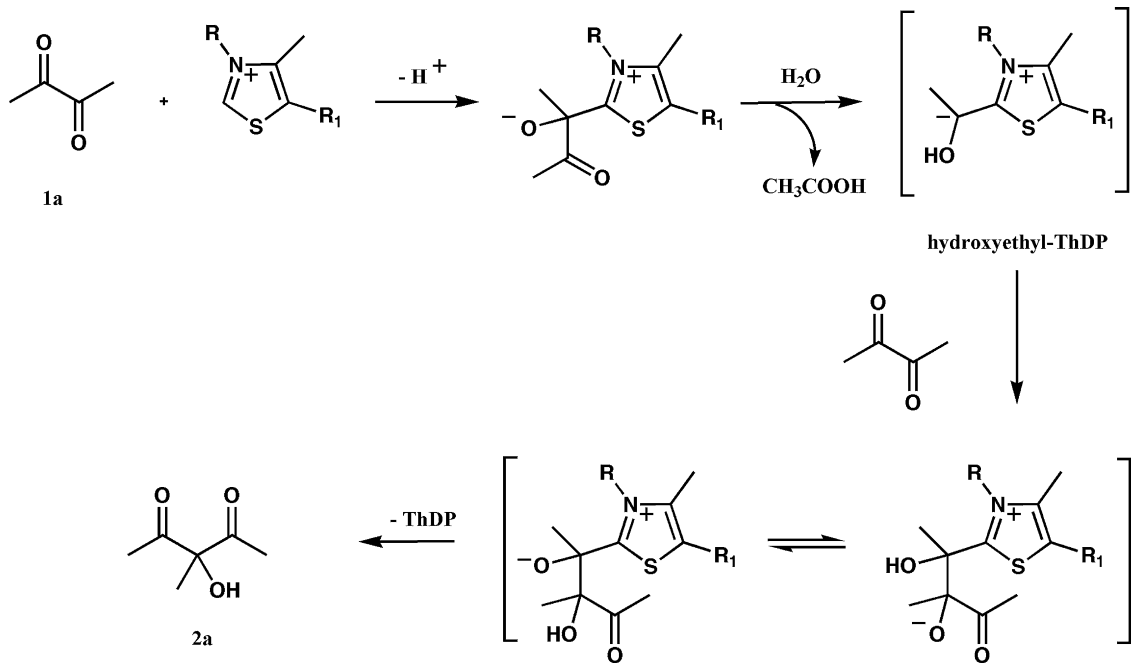
Scheme 1. ThDP-mediated C–C bond formation.

Table 1
AAS-catalyzed homo-coupling reactions of 1,2-diketones **1a–e**.



1,2-Diketone **1**	α-Hydroxy-1,3-diketone **2** (yield %)	α-Hydroxy-1,3-diketone **3** (yield %)
1a	**2a** (57)	
1b	**2b** (60)	
1c	**2c** (30, ee 70%)[a]	**3c** (25)[a]
1d	**2d** (42, ee 67 %)[a]	**3d** (19)[a]
1e	**2e** (45, ee 76%)	

[a]The yields are calculated on the basis of the ratio obtained in the mixture.



Scheme 2. AAS-catalyzed conversion of diacetyl to acetylacetoin.

2. Experimental

2.1. Analytical methods

GC analyses were performed on a Carlo Erba 6000, equipped with a FID detector and a fused capillary column Megadex 5 (25 m × 0.25 mm) containing dimethyl-*n*-pentyl-β-cyclodextrin on OV 1701 (from Mega snc), helium as carrier gas (80 kPa). The mass spectra were obtained using a Varian 4000 GC/MS/MS equipped with chiral column Megadex 5, using the same conditions described for GC analyses. NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are given in parts per million from Me_4Si as internal standard. Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter.

2.2. Preparation of the cell free extract

B. stearothermophilus ATCC2027 was cultured in a medium (200 mL in a 500 mL Erlenmeyer flask) containing meat extract (10 g/L), polypeptone (10 g/L), NaCl (5 g/L) and 3-hydroxy-2-butanone (5 g/L). After 48 h growth at 110 rpm the cells (2 g, wet weight) were harvested by centrifugation (6000 rpm, 10 min), washed with 150 mM NaCl solution (50 mL) and suspended in 50 mM phosphate buffer at pH 6.5 (50 mL). The suspension was treated at high pressure (1380 bar) with a French press and then centrifuged (15,000 rpm, 20 min, 5 °C). The supernatant (46 mL) was used without further purification to catalyze the coupling reactions.

2.3. General procedure for AAS-catalyzed homo-coupling reaction of 1,2-diketones ***1a–e***

The cell free extract (46 mL) was added to a solution of diketones **1** (3 mmol), thiamine diphosphate (15 mg, 35 μmol) and magnesium sulphate (10 mg, 83 μmol) in 50 mM phosphate buffer at pH 6.5 (50 mL). The reaction was gently shaken at 30 °C for 14 h and then heated (80 °C, 20 min). After removing the precipitate by centrifugation (10,000 rpm, 20 min) the solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (40 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed on silica gel (chloroform/*n*-hexane 8:2 as eluent) to afford the products **2** and **3** (Table 1).

2.3.1. Homo-coupling reaction of 2,3-butanedione ***1a***

GLC analysis; temp 60–64 °C (1 °C/min) 64–200 °C (2 °C/min), retention time (min): **1a**, 3.0; **2a**, 15.1.

3-Hydroxy-3-methyl-2,4-pentanedione **2a** [15]: colourless oil; 0.11 g, 57%; ^{1}H NMR (300 mHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 2.30 (s, 6H, $2CH_3CO$), 4.70 (s, 1H, OH).

2.3.2. Homo-coupling reaction of 3,4-hexanedione ***1b***

GLC analysis; temp 80–200 °C (1.5° C/min), retention time (min): **1b**, 5.2; **2b**, 22.5.

4-Ethyl-4-hydroxy-3,5-heptanedione **2b**: colourless oil; 0.15 g, 60%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, J = 7.5 Hz, CH_3), 1.04 (t, 6H, J = 7.5 Hz, $2CH_3$), 2.04 (q, 2H, J = 7.5 Hz, CH_2), 2.51 (dq, 2H, J = 21 Hz, J = 7.5 Hz, CH_2), 2.73 (dq, 2H, J = 21 Hz, J = 7.5 Hz, CH_2), 4.65 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 7.3, 7.4, 29.8, 30.6, 90.9, 210.2.

Anal calcd for $C_9H_{16}O_3$: C, 62.77%, H, 9.36%; Found C, 62.90%, H, 9.39%.

2.3.3. Homo-coupling of 2,3-pentanedione ***1c***

GLC analysis; temp 80–200 °C (1.5° C/min), retention time (min): **1c**, 5.1; **3c**, 11.6; **2c**, 15.4 and 15.9.

3-Hydroxy-3-methyl-2,4-hexanedione **2c** and *3-ethyl-3-hydroxy-2,4-pentanedione* **3c** are obtained in 1.2:1 mixture (yield of the mixture 55%). Pure sample of **2c** was obtained by flash chromatography on silica gel (*n*-hexane/AcOEt 10:1 as eluent).

3-Hydroxy-3-methyl-2,4-hexanedione **2c**: colourless oil; 65 mg, 30%; $[\alpha]_D^{20}$ = +15 (*c* 0.5 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, 3H, J = 7.5 Hz, CH_3), 1.55 (s, 3H, CH_3), 2.27 (s, 3H, CH_3CO), 2.51 (dq, 1H, J = 21 Hz, J = 7.5 Hz, CH_2), 2.73 (dq, 1H, J = 21 Hz, J = 7.5 Hz, CH_2), 4.65 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 7.5, 22.8, 24.5, 87.4, 207.4, 210.2; GC–MS: retention time

(min) 15.4 and 15.9, ee 70%; MS (70 eV, EI); *m/z* (%) 145 (≤1%) $[M+H]^+$, 102 (27%) $[(MH)–CH_3CO]^+$, 88 (100%) $[(MH)–C_2H_5CO]^+$, 57 (25%), 43 (30%).

Anal calcd for $C_7H_{12}O_3$: C, 58.32%; H, 8.39%. Found C, 58.42%; H, 8.37%.

3-Ethyl-3-hydroxy-2,4-pentanedione **3c**: colourless oil; 50 mg, 25%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (t, 3H, J = 7.5 Hz, CH_3), 2.05 (q, 2H, J = 7.5 Hz, CH_2), 2.27 (s, 6H, 2 CH_3CO); 4.7 (br s, 1H, OH).

2.3.4. Homo-coupling of 2,3-hexanedione *1d*

GLC analysis; temp 80–200 °C (1.5° C/min), retention time (min): **1d**, 4.9; **3d**, 15.9; **2d**, 20.8 and 20.9.

3-Hydroxy-3-methyl-2,4-heptanedione **2d** and *3-acetyl-3-hydroxy-2-hexanone* **3d** are obtained in 2.2:1 mixture (yield of mixture 61%). Pure samples of **2d** and **3d** were obtained by flash chromatography on silica gel (*n*-hexane/AcOEt 10:1 as eluent).

3-Hydroxy-3-methyl-2,4-heptanedione **2d**: colourless oil; 99 mg, 42%; $[\alpha]_D^{20}$ = +3 (*c* 0.5 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.5 Hz, CH_3), 1.56 (s, 3H, CH_3), 1.6 (m, 2H, CH_2), 2.25 (s, 3H, CH_3CO), 2.49 (dt, 1H, J = 17.5 Hz, J = 7.5 Hz, CH_2), 2.68 (dt, 1H, J = 17.5 Hz, J = 7.5 Hz CH_2,), 4.75 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.5, 16.8, 22.6, 24.6, 38.6, 87.6, 207.4, 209.5; GC–MS: retention time (min) 20.8 and 20.9, ee 67%; MS (70 eV, EI): *m/z* (%) 159 (≤1%) $[M+H]^+$, 116 (21%) $[(MH)–CH_3CO]^+$, 88 (100%) $[(MH)–C_3H_7CO]^+$, 71 (37%), 43 (46%).

Anal calcd for $C_8H_{14}O_3$: C, 60.74%; H, 8.92%. Found: C, 60.61%; H, 8.89%.

3-Acetyl-3-hydroxy-2-hexanone **3d**: colourless oil; 45 mg, 19%; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.95 (t, 3H, J = 7.5 Hz, CH_3); 1.22 (m, 2H, CH_2); 1.93 (m, 2H, CH_2); 2.24 (s, 6H, 2 CH_3CO), 4.65 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 16.6, 25.3, 38.4, 91.1, 207.5.

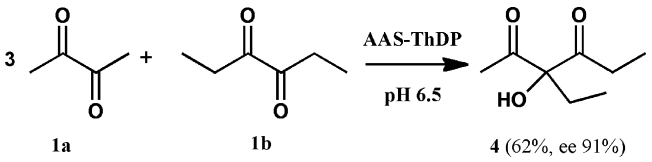
Anal calcd for $C_8H_{14}O_3$: C, 60.74%; H, 8.92%. Found: C, 60.69%; H, 8.95%.

2.3.5. Homo-coupling reaction of 1-phenyl-1,2-propanedione *1e*

GLC analysis; temp 100–200 °C (5° C/min), retention time (min): **1e**, 10.9; **2e**, 16.6 and 16.7.

2-Hydroxy-2-methyl-1-phenyl-1,3-butanedione **2e**: colourless oil; 0.13 g, 45%; ee 40%; $[\alpha]_D^{20}$ = +13 (*c* 0.5 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.7 (s, 3H, CH_3), 2.2 (s, 3H, CH_3CO), 5.0 (br s, 1H, OH), 7.4–8.2 (m, 5H, Ph); ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.4, 24.7, 85.8, 128.6, 129.8, 133.6, 133.9, 197.9, 206.5; GC–MS: retention time (min) 16.6 and 16.7, ee 76%; MS (70 eV, EI): *m/z* (%) 193 (2%) $[M+H]^+$, 150 (24%) $[(MH)–CH_3CO]^+$, 105 (100%), 77 (56%).

Anal calcd for $C_{11}H_{12}O_3$: C, 68.74%; H, 6.29%. Found: C, 68.59%, H, 6.31%.



Scheme 3. AAS-mediated cross-coupling reaction of diketones **1a** and **1b**.

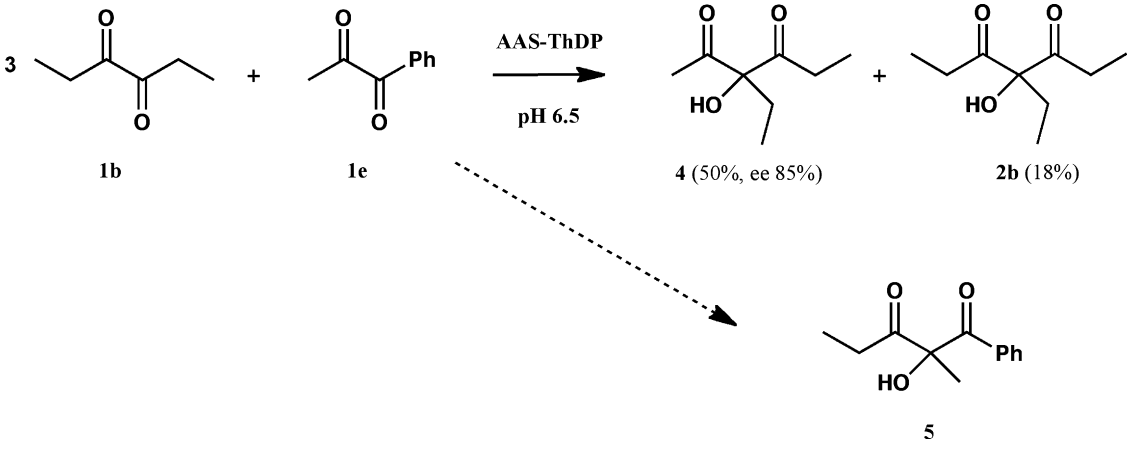
2.4. AAS-catalyzed cross-coupling reaction of 1,2-diketones *1a* and *1b*

The cell free extract (10 mL) was added to a solution of **1a** (0.46 g, 5.4 mmol), **1b** (0.2 g, 1.8 mmol), thiamine diphosphate (5 mg, 12 μmol) and magnesium sulphate (3 mg, 25 μmol) in 50 mM phosphate buffer at pH 6.5 (10 mL). The reaction was gently shaken at 30 °C for 48 h and then worked up as described for the homo-coupling reactions. GLC analysis; temp 80–200 °C (1.5° C/min), retention time (min): **2a**, 9.3; **4**, 19.3 and 19.7; **2b**, 22.5. After chromatography of the residue on silica gel (*n*-hexane/AcOEt 10:1 as eluent) *3-ethyl-3-hydroxy-2,4-hexanedione* **4** (Scheme 3) was obtained as colourless oil: 0.176 g (62%); $[\alpha]_D^{20}$ = +49.8 (*c* 1.6 g/100 mL, CH_2Cl_2); ^{1}H NMR (300 mHz, $CDCl_3$): δ 0.8 (t, 3H, J = 7.5 Hz, CH_3), 1.0 (t, 3H, J = 7.5 Hz, CH_3), 2.0 (q, 2H, J = 7.5 Hz, CH_2), 2.3 (s, 3H, CH_3CO), 2.5 (dq, 1H, J = 20 Hz, J = 7.5 Hz, CH_2), 2.7 (dq, 1H, J = 20 Hz, J = 7.5 Hz, CH_2), 4.6 (br s, 1H, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 7.3, 7.4, 25.0, 29.6, 30.9, 91.1, 207.4; 210.2. GC–MS: retention time (min) 19.3 and 19.7, ee 91%; MS (70 eV, EI): *m/z* (%) = 159 (1%) $[M+H]^+$, 116 (50%) $[(MH)–CH_3CO]^+$, 102 (100%) $[(MH)–C_2H_5CO]^+$, 87 (90%).

Anal calcd for $C_8H_{14}O_3$: C, 60.74%; H, 8.92%. Found: C, 60.70%; H, 8.94%.

2.5. AAS-catalyzed cross-coupling reaction of 1,2-diketones *1b* and *1e*

The cell free extract (10 mL) was added to a solution of **1b** (0.5 g, 4.4 mmol), **1e** (0.22 g, 1.5 mmol), thiamine diphosphate (5 mg, 12 μmol) and magnesium sulphate (3 mg, 25 μmol) in 50 mM phosphate buffer at pH 6.5 (10 mL). The reaction was gently shaken at 30 °C for 48 h and then worked up as described for the homo-coupling reactions. After chromatography of the residue on silica gel (*n*-hexane/AcOEt 10:1 as eluent) *3-ethyl-3-hydroxy-2,4-hexanedione* **4** (0.12 g, 50%, ee 85%) was obtained (Scheme 4).



Scheme 4. AAS-mediated cross-coupling reaction of diketones **1b** and **1e**.

3. Results and discussion

B. stearothermophilus AAS is an inducible enzyme and it can be easily obtained from the cells cultivated on a 3-hydroxy-2-butanone (acetoin) rich medium [11]. The cell free extract, obtained after high-pressure extrusion of a bacterial cells suspension in phosphate buffer at pH 6.5, was used without any purification to directly catalyze the reactions. The homo-coupling reactions were carried out by adding catalytic amount of ThDP and $MgSO_4$ to a solution of the selected α-diketone in the cell free extract. After simple work up and chromatography the 2-alkyl-2-hydroxy-1,3-diketones **2** and **3** were obtained in 19–60% yield. The results are reported in Table 1.

The symmetric 2,3-butanedione **1a** and 3,4-hexanedione **1b** afforded 3-hydroxy-3-methyl-2,4-pentanedione (acetylacetoin) **2a** and 4-ethyl-4-hydroxy-3,5-heptanedione **2b** in 57% and 60% yield, respectively. On the basis of this result it is possible to assert that AAS is able to transfer both the acetyl and propionyl carbanion.

On the contrary the reactions of the non-symmetric diketones **1c–e** gave only the products **2c–e** and **3c** and **3d** derived from the acetyl anion transfer. This suggested a higher migratory aptitude of this group with respect to propionyl or other alcanoyl moieties. In particular the homo-coupling of 2,3-pentanedione **1c** gave a 1.2:1 mixture of the regioisomers **2c** and **3c** (yield of the mixture 55%) arising from the attack of the acetyl carbanion at C-2 and C-3 of **1c**, respectively. Flash chromatography of the mixture afforded the chiral 3-hydroxy-3-methyl-2,4-hexanedione **2c** with 70% enantiomeric excess, determined by GC–MS on chiral column.

Similar results were obtained by the homo-coupling reaction of 2,3-hexanedione **1d** that gave a 2.2:1 ratio mixture of regioisomeric **2d** and **3d** (yield of mixture 61%) probably because of the steric hindrance of the propyl moiety. Also in this case the chiral 3-hydroxy-3-methyl-2,4-heptanedione **2d** was separated from **3d** by flash chromatography and the enantiomeric excess (67%) was determined by GC–MS on chiral column. This behaviour was confirmed by the reaction with 1-phenyl-1,2-propanedione **1e** that produced only the chiral **2e** (45%, ee 76%). The sole formation of this product was probably favoured by the low electrophilicity of the benzylic carbonyl in addition to the less hindrance of C_2-position. Furthermore, the inability of AAS to transfer the benzoyl carbanion was demonstrated by the reaction with 1,2-diphenyl-1,2-ethanedione that did not give any homo-coupling product.

On the basis of these results the synthetic potential of *B. stearothermophilus* AAS was investigated using a donor different from the acceptor (cross-coupling reaction). The reaction of diketones **1a** and **1b** in different ratios produced the cross-coupling product 3-ethyl-3-hydroxy-2,4-hexanedione **4** together with the previously observed homo-coupling product **2b** (Fig. 1). With an excess of **1b** the homo-coupling product **2b** prevailed over **4**. The best conversion of **1b** to the chiral **4** (62%, ee 91%) was obtained using a 3:1 ratio of **1a** and **1b** (Scheme 3).

On the contrary, the cross-coupling between diketones **1b** and **1e**, using an excess of **1b** (3 equiv.) in an attempt to transfer a propionyl carbanion from **1b** to **1e** did not afford the "expected cross-coupling product 5" but 3-ethyl-3-hydroxy-2,4-hexanedione **4** (50%, ee 91%) as main product and 4-ethyl-4-hydroxy-3,5-heptanedione **2b** (18%) as minor product (Scheme 4). This result confirmed the higher migratory aptitude of acetyl *vs* propionyl anion and prevented the possibility to use potential acetyl donors as acceptor for other acyl anion moieties.

On the other hand, attempts to employ ketones, acetaldehyde and benzaldehyde as substrates either for homo- or cross-coupling reactions did not afford any significant results. The absolute configuration of the new compounds **2c**, **2d**, **2e** and **4** is under investigation.

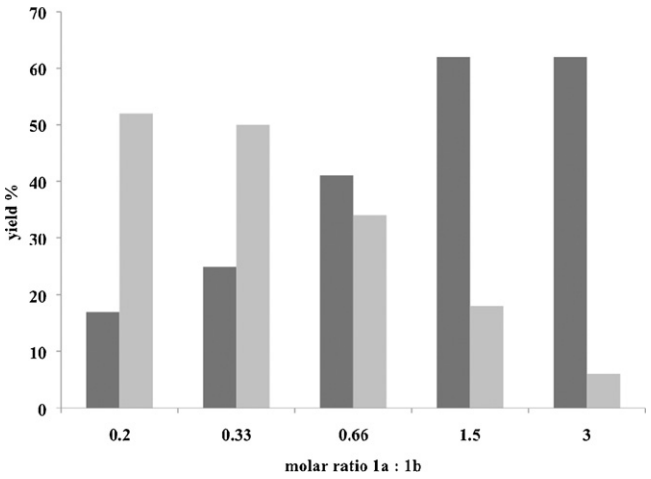


Fig. 1. Product distribution of the cross-coupling reaction of **1a** and **1b**: (■) compound **4**; (▒) compound **2b**.

4. Conclusions

To our knowledge this is the first synthetic application of a ThDP-depending enzyme that, using a ketone as acceptor of the ThDP-activated acyl carbanion, allows the formation of tertiary substituted alcohols. *B. stearothermophilus* AAS catalyzes the homo-coupling reactions of the 1,2-diketones **1a–e** furnishing a new enzymatic strategy for the synthesis of 2-alkyl-2-hydroxy-1,3-diketones **2a–e** (30–60%) and **3c** and **3d** (19–25%). Except for **2a**, all these 1,3-diketones are new compounds that have been fully characterized. All chiral compounds (i.e. **2c**, **2d** and **2e**) are obtained in good enantiomeric excesses (70%, 67%, and 76%, respectively). The AAS is also employed in the cross-coupling reactions of diketones **1a** and **1b** to give the 1,3-diketone **4**. The best yields of **4** (62%, ee 91%) are obtained with 3 equiv. of **1a**. Surprisingly the cross-coupling reaction of diketones **1b** and **1e** (3:1 ratio) does not afford the "expected 2-hydroxy-2-methyl-1-phenyl-1,3-pentanedione **5**" but the 1,3-diketone **4** confirming the higher migratory aptitude of acetyl *vs* propionyl anion. The enantiomeric excesses of all chiral compounds are determined by chiral GC/MS spectrometry and the absolute configuration is still under investigation.

Finally, the products obtained by AAS-mediated homo- and cross-coupling reactions are multidentate compounds containing a chiral or a prochiral hydroxylated carbon centre, interesting and promising building blocks for asymmetric synthesis [13–15].

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